GENE THERAPY ADVISORY COMMITTEE

SEVENTH ANNUAL REPORT

January 2000 – December 2000

Health Departments of the United Kingdom
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FOREWORD

It is a source of pride and pleasure to me that the United Kingdom continues to encourage and facilitate gene therapy research, within a regulatory framework (GTAC), where safety of and the welfare of patients is of paramount importance. The year 2000 saw an unprecedented three-fold increase in the number of new gene therapy studies. By the end of the year, more than sixty gene therapy trials were either completed, underway or in the process of being approved by GTAC. Thus, the United Kingdom continues to maintain the lead position for gene therapy research in Europe. More than fifty percent of European gene therapy clinical trials take place here.

There is continued interest in gene therapy research studies for the management of various forms of cancer. While studies involving monogenic disorders barely represent ten percent of GTAC approvals, there is a sustained commitment to diseases like X-linked Severe Combined Immunodeficiency (X-SCID). Another area of development has been the application of gene therapy as an approach for the treatment of diseases acquired during the lifetime of the patient, such as peripheral arterial occlusive disease and HIV infection. In the near future, one might expect that, as investigators' familiarity with gene therapy progresses, a broader spectrum of diseases will become the focus for gene therapy studies. The development of more efficient gene therapy vectors, particularly with more improved systems for the control of gene expression, will permit new approaches to the treatment of diseases previously beyond the scope of gene therapy research. At present the success rate for gene therapy is modest but the logic behind it is compelling. Everything we know about molecular biology tells us that gene therapy will work. We can look forward to an exciting future.

With the increase in the committee's workload, I was delighted to welcome several new members to the committee: Professor Alex Markham, Professor David Harrison, Dr Andrew Lever, Dr David Crosby and the Reverend Dr Lee Rayfield. Their varied expertise greatly complements the wide experience acquired by GTAC since 1993. I also thank retiring members: Professor Michael Steele, Professor Patrick Johnson, Dr. Brenda Gibson, Reverend Dr Keith Denison, Professor Anthony Dayan, Professor John Burn and Professor Elizabeth Anionwu for their constructive contributions to GTAC over the years. I would also like to thank the Secretariat that supports the committee. Members of the Committee owe a great deal to their expertise.

Professor Norman C Nevin, GTAC Chairman

GTAC Seventh Annual Report

PART 1

SECTION 1: PROTOCOLS APPROVED BY GTAC IN 2000

1.1 This year GTAC moved to a graded system of review, based on the novelty and complexity of the proposal. Of the 21 new protocols submitted to GTAC during 2000, 18 were considered in full committee and three protocols were approved by Chairman's Action following the appropriate level of review. Two submissions were subsequently withdrawn and approval for one study denied.

INTRAEPITHELIAL NEOPLASIA

1.2 Human Papilloma virus (HPV) causes warts. There are some types of HPV that infect the genital area and in fact HPV is the most common viral sexually-transmitted disease in the world. HPV DNA is often found in biopsies from patients presenting with cancers of the cervix, vulva and anus and an association between the virus and malignancy has been proposed. HPV is associated with at least half of the reported cases of vulval intraepithelial neoplasia, while in the case of ano-genital cancers, over 80% harbour HPV. The reported incidence of this Vulval Intraepthelial neoplasia doubled from the mid-1970's to the mid-1980's from 1.1 to 2.1 cases per 100,000 women.

Use of recombinant Vaccinia vaccine (TA-HPV) to treat Vulval intraepithelial neoplasia III (GTAC 12C). St Mary's Hospital, Manchester.

1.3 This vaccination approach was first approved by GTAC in June 1995. The objectives of the original trial were to establish the safety, as well as the immunogenicity, of a vaccinia-based vector (TA-HPV) in eight patients with late stage cervical cancer (GTAC 012). GTAC gave approval in May 1997 to recruit early stage cervical cancer patients (CIN3). That proposal aims to enhance the recognition of HPV E6 and E7 proteins in cervical carcinomas, using TA-HPV, thus offering the possibility of recruiting the patients immune system into the destruction of tumour cells.

1.4 TA-HPV has been developed from Vaccinia virus, the live vaccine of which has been used extensively in smallpox eradication programmes. TA-HPV is a genetically modified vaccine which has muted ability to multiply in human cells. It is designed to deliver the E6 and E7 genes from HPV to the sites of infection. By injecting this engineered virus into patients muscle, it is hoped that the patients' immune system will be coaxed to recognise HPV-infected cells (expressing E6 and E7 proteins) as "foreign" and mount an attack on them. In this way, HPV-infected cells of the vulva, with the potential to become cancerous, may be destroyed by the body's own defences. A total of 30 subjects with grade III Vulva intraepithelial neoplasia are to be enrolled in the trial. GTAC formally approved this clinical trial in April.

Use of a recombinant Vaccinia vaccine (TA-HPV) to treat Ano-genital intraepithelial neoplasia III (GTAC12D). Addenbrooke's Hospital, Cambridge.

1.5 This study is analogous to the one described above. The study vector is identical, as is the mode of administration. The patient group, in this case, was comprised of those suffering from ano-genital intraepthileial neoplasia III, with a total of 30 to be recruited into the trial. GTAC gave formal approval for this trial to proceed in April 2000.

LIVER CANCER

1.6 The liver is a common site of cancer when it spreads from other tissues such as lung, breast, colon and rectum. Cancer cells detach from the original cancer site and travel via the bloodstream or lymph system to take up residence in the liver. For patients with metastatic liver tumours, chemotherapy provides only modest benefit, mainly in the form of pain relief or easing of other symptoms.

A phase I/II study of hepatic artery infusion with WTP53-CMV-AD in primary metastatic malignant liver tumours. (GTAC028). Hammersmith Hospital, London.

1.7 The human p53 gene suppresses tumour growth and loss of the wild-type (normal) function of p53 is associated with the uncontrolled growth of many human cancers. By introducing a normal copy of the p53 gene

into p53 deficient tumour cells it has been shown that tumour growth can be reduced and apoptosis (programmed cell death) promoted.

1.8 Adenoviruses cause infections of the respiratory tract. The vector wtp53-CMV-Ad is a replication-defective adenovirus (altered so that it cannot cause infections) which contains a gene for normal (wild-type) p53 (expression is under the control of the human cytomegalovirus immediate early promoter-enhancer).

1.9 In this phase I study at the Hammersmith Hospital, it was proposed to administer the vector by infusion via the hepatic artery to patients who have incurable metastatic malignant tumours of the liver, which are p53 deficient. The study sought to determine the maximum safe dose of the vector and to determine its efficacy in the treatment of these tumours.

1.10 In October 1998 GTAC gave conditional approval subject to receiving a satisfactory response on a number of points, including amendments to the patient information leaflet and consent form. In light of a number of issues raised, the proposers announced to GTAC in October 2000 that they no longer intended to conduct this trial and withdrew their submission.

GLIOMA

1.11 Gliomas account for half of all brain tumours and the most frequent of these is glioblastoma (GB). In the UK approximately 4,000-5,000 patients with brain tumours are diagnosed each year. The most common glioma is *glioblastoma multiforme*. Current treatments for glioblastoma (radiotherapy, chemotherapy, surgery) are *palliative* and rarely alter the long term prognosis. Patients with glioblastoma have a very poor outlook despite surgical removal of their tumours and aggressive post-operative radiotherapy. Despite therapy, including surgery, the median survival for patients is 9 to 10 months. Five year survival is extremely rare.

A study of the safety of the modified *Herpes simplex* virus (HSV 1716) when injected into tumour bearing brain following resection of recurrent or newly diagnosed high grade glioma (GTAC 18B). Beatson Oncology Centre, Glasgow.

1.12 The *Herpes simplex* virus causes infections such as cold-sores, genital infections and a rare brain infection (encephalitis). HSV 1716 is a modified form of this virus which cannot infect cells that are not themselves rapidly dividing. Most of the cells in the normal brain do not divide and therefore this virus should not be able to infect them. Tumour cells are rapidly dividing so that HSV 1716 should be able to selectively infect these cells and hopefully kill them.

1.13 In December 1996 GTAC approval was granted for a dose escalation study of intratumoural injection of HSV 1716 in patients with recurrent glioma. Following submission of a report back to GTAC (which showed the treatment to be well tolerated – no patient suffered toxicity/infection with HSV requiring treatment) approval was granted to recruit up to 12 patients with newly diagnosed glioma.

1.14 The eventual utility of this approach is likely to be by injection into residual tumour tissue left behind in adjacent normal brain tissue following tumour resection. In a procedure that will extend the tumour resection operating time by 5-10 minutes, HSV 1716 will be injected into the tumour cavity. Although the primary objective will be to assess safety, the gene therapy recipients will be matched up to a similar group of patients undergoing routine surgery in order to give an indication of efficacy and aid in future study design.

1.15 GTAC reviewed this proposal at their meeting in July 2000 and granted the project conditional approval. Final approval was granted in January 2001.

MULTIPLE MYELOMA

1.16 Multiple myeloma (MM) is a tumour of the bone marrow which can lead to major complications such as bone marrow suppression, destruction of the skeleton and damage to the kidneys. Bone marrow transplantation from a matched donor is probably the only treatment that offers the possibility of a cure. It is thought that bone marrow transplantation may be effective because the transplant eliminates the myeloma by mounting an immune response against the tumour. This effect may be enhanced by the later infusion of donor lymphocytes. These are white blood cells isolated from donors peripheral blood that help in fighting infection and disease.

A pilot study of donor idiotypic vaccination for the purpose of targeted post-transplant immunotherapy following allogenic bone marrow transplantation for multiple myeloma (GTAC 029B). Department of Haematology and Oncology, Royal Bournemouth Hospital and Royal Hampshire Hospital.

1.17 This study is a developmenmt of a previously approved protocol. The original study was designed to assess the feasibility of vaccinating patients with follicular lymphoma against a tumour specific antigen derived from their own tumour (known as an "idiotype"). In this study up to 5 patients will be recruited who have undergone a bone marrow transplant from a sibling but who have either not achieved a complete remission or who have relapsed after having previously achieved a complete remission. The investigators propose to vaccinate the donor against the patient's idiotype prior to harvesting the donor's now "educated" lymphocytes for infusion (but after the bone marrow transplant). It is hoped in this way that the donor's lymphocytes anti-myeloma effect will be enhanced.

Proposal to immunise bone marrow transplant donors against tumour antigens of the transplant recipient using a DNA vaccine (GTAC 029C). Department of Haematology and Oncology, Royal Bournemouth Hospital and Royal Hampshire Hospital.

1.18 This study is a development of a previously approved protocol. The original study was designed to assess the feasibility of vaccinating patients with follicular lymphoma against a tumour specific antigen derived from their own tumour (known as an "idiotype"). In this study, up to 5 patients will be recruited who have undergone a bone marrow transplant from a sibling but who have either not achieved a complete remission or who have relapsed after having previously achieved a complete remission. The investigators propose to vaccinate the donor against the patient's idiotype prior to harvesting the donor's now "educated" lymphocytes for infusion (but after the bone marrow transplant). It is hoped that in this way the donor's lymphocytes anti-myeloma effect will be enhanced.

1.19 The protocol was considered by GTAC at their February 2000 meeting and received approval in August 2000.

Proposal to immunise bone marrow transplant donors against tumour antigens of the transplant recipient using a DNA vaccine (GTAC 029C). Department of Haematology and Oncology, Royal Bournemouth Hospital and Royal Hampshire Hospital.

1.20 This study is a development of previously approved protocols of DNA idiotype vaccines in follicular lymphoma (GTAC 029A) and multiple myeloma (GTAC 029B). Both studies were designed to assess the feasibility of vaccinating patients against a tumour specific antigen (idiotype) derived from their own tumour.

1.21 Bone marrow transplants are a potential therapeutic option for patients with follicular lymphoma. Graft-Versus-Host Disease (GVHD) is a common and serious complication of bone marrow transplantation where there is a reaction of donated bone marrow against a patient's own tissue. Associated with GVHD is an immune attack on the tumour, which is probably the way such transplants cure malignant disease. Here it is proposed to immunise healthy donors against the recipients tumour with the aim of enhancing the grafted immune system's ability to eliminate the patients tumour. DNA specific for the patient's tumour (idiotype) is inserted into a vector to introduce that into muscle cells. The patient would then produce tumour specific antigens and thereby increase the immune response to the tumour. A total of five donors are to be immunised with two matched patients already identified.

1.22 The proposal was considered by GTAC at their meeting in May 2000 and granted approval in August 2000.

LEUKAEMIA

1.23 Chronic myeloid leukaemia is a type of cancer of the blood cells. It can be treated by allogeneic bone marrow transplant (BMT) in which the patient's bone marrow is destroyed and replaced with bone marrow from a donor with

healthy bone marrow whose tissue is (almost) the same as the patient's. Graft versus Host Disease (GVHD) is a potentially fatal complication of allogeneic BMT which occurs in around 40% of sibling grafts and 80% of unrelated donor transplants. GVHD is mediated by a type of white cell in the BMT called T-lymphocytes and can be prevented by the removal of this type of cells from the donor marrow prior to the transplant or treated using immunosuppressive drugs.

1.24 The treatment of choice for a patient who relapses after BMT is the infusion of donor lymphocytes (DLI) sourced from the blood of the original BMT donor. Although this additional treatment may lead to a second remission, it too carries a risk of GVHD. This GVHD can also be treated using immunosuppressive drugs, but such treatments may both inactivate the ability of the graft to eliminate residual cancer cells (graft-versus-cancer effect) and/or render the patient susceptible to infection.

Phase I/II study of idiotypic vaccination for chronic lymphocytic leukaemia using a genetic approach (GTAC 029D). Royal Bournemouth Hospital and Royal Hampshire Hospital.

1.25 GTAC considered and approved a Phase I/II study of idiopathic (Id) vaccination for follicle centre lymphoma in May 1999. Follicular centre lymphoma is a slowly progressing malignant disease which shows frequent spontaneous remissions. It tends to respond to conventional treatments but over a period of months or years, the remissions become shorter until the disease no longer responds to treatment. The original proposal aimed to introduce DNA specific for the patient's tumour (idyotype) into a vector and to introduce that into muscle cells. The patient would then produce tumour specific antigens and thereby increase the immune response to the tumour.

1.26 Bone marrow transplants are a potential therapeutic option for patients with follicular lymphoma. GVHD is a common and serious complication of bone marrow transplantation where there is a reaction of donated bone marrow against a patient's own tissue. Associated with GVHD is an immune attack on the tumour, which is probably the way that such transplants cure malignant disease. The aim of this study is to immunise healthy donors against the recipient's tumour with the aim of enhancing the grafted immune system's ability to eliminate the patient's tumour. A total of 5 donors were to be recruited.

1.27 GTAC considered this proposal at their meeting in February 2000 and granted full approval in April 2000.

Treatment of leukaemic relapse after allogeneic stem cell transplantation by HSV-*tk* transduced donor lymphocyte transfusions (GTAC 044). Hammersmith Hospital, London.

1.28 *Herpes simplex* is a retrovirus which can cause infections such as cold-sores, genital infections and encephalitis. For this project, the investigators propose to genetically modify donor lymphoctyes with a virus carrying the *Herpes simplex* thymidine kinase gene (HSK-tk). Cells expressing this gene are susceptible to killing by a drug called Ganciclovir. Should the patient develop Graft Versus Host Disease (GVHD) following Donor Lymphocyte Infusion (DLI), the patient would be given ganciclovir in an attempt to kill off the transduced donor lymphocytes without immunosuppressing the patient.

1.29 GTAC considered this proposal at their meeting in October 2000 and granted conditional approval. Final, approval was granted in August 2001.

OVARIAN CANCER

1.30 Ovarian cancers are a major cause of death for women in the United Kingdom. It was estimated that more than 6,000 new cases of ovarian cancer would be diagnosed in the UK, and 4,500 women would die from this disease this year. Ovarian cancer is curable in its earliest stages, as it is highly responsive to chemotherapy. However an overwhelming majority of patients are diagnosed in the advanced stage. Over the past two decades, the five-year survival rate for this disease has improved only marginally from 34% to 39%.

Gene therapy protocol for the use of MetXia-P450 for the treatment of ovarian cancer (GTAC 030). Northern General Hospital, Sheffield.

1.31 MetXia-P450 is a retroviral vector carrying the human gene for cytochrome P450. This is an enzyme that converts the pro-drug cyclophosphamide to an agent which is highly toxic for dividing cells, such as tumour cells. The investigators proposed to administer MetXia-P450 by a single intraperitoneal injection prior to chemotherapy (cisplatin and cyclophosphamide). In this way, the investigators hope to increase the level of the active drug locally in the transduced tumour tissue and therefore enhance the tumour killing capacity with relatively low doses of cyclophosphamide. Cyclophosphamide has been used extensively for the treatment of a number of cancers, including ovarian cancer. Under these circumstances the liver activates the drug which is then dispersed to tumours via the blood stream. A major limitation of the conventional approach is that low doses do not kill all the tumour cells whereas high doses are toxic to the bone marrow of the patient. Using this approach investigators should be able to administer low levels of the drug systemically, which should then be converted to its highly toxic form within transduced tumour cells.

1.32 Patients were to be divided into four groups, the first two receiving MetXia P450 and a therapeutic dose of carboplatin. Following surgery samples of their tumour would be assessed to see which dose had resulted in the greatest uptake of virus by the tumour cells. Groups 3 and 4 would then receive the dose which resulted in maximum gene transfer and also carboplatin plus cyclophosphamide.

1.33 GTAC considered this proposal at their meeting on 12 May 1999. Conditional Approval was granted subject to receipt of a satisfactory response to a number of points and amendments to the protocol. GTAC approved this clinical trial proposal in February 2000.

PERIPHERAL ARTERIAL OCCLUSIVE DISEASE

1.34 Peripheral Arterial Occlusive Disease (PAOD) occurs when atherosclerosis blocks blood flow through the large arteries of the lower limbs. This results in ischemia or loss of oxygen supply because of the poor blood circulation. This condition is highly disabling and painful for those afflicted, leading to tissue damage (the appearance of ulcers), necrosis (gangrene) and ultimately the requirement for amputation of the affected limb. Risk factors associated with the disease including smoking, diabetes, distal arterial disease, high blood pressure and hyperlipidemia. The disease afflicts up to 500 per million each year in the developed world.

1.35 PAOD patients have few treatment options especially when attempts such as balloon angioplasty have failed to alleviate the condition. One of the few remaining options is amputation.

The safety and effects of Ad5.1 mediated human FGF-4 gene transfer in patients with peripheral arterial occlusive disease (PAOD) Fontaine stage III (Phase I i.m.). (GTAC 036). St. Georges Hospital, London.

1.36 A novel therapeutic approach to this disease involves trying to induce new blood vessels in the limb muscle to meet its oxygen requirements. This process is referred to as *angiogenesis*. Fibroblast Growth Factor-4 (FGF-4) is a protein which has been shown to stimulate blood vessel formation in pre-clinical studies. The investigators plan to use an adenoviral vector (similar to viruses which cause colds but disabled so that they cannot replicate) to deliver the gene for FGF-4 into the muscles of patients' affected leg (this vector is called Ad5.1FGF-4).

1.37 It is hoped that the cells of the patient's muscles will make the FGF-4 protein thereby promoting the formation of blood vessels. If this is successful, the progression of the disease may be slowed or halted and also that the patient's symptoms might improve (healing of leg ulcers and reduction in pain).

1.38 This is a "double-blind, randomised, placebo-controlled study" which means that some of the patients would be injected with Ad5.FGF-4 and some with a placebo (consisting only of the liquid used to suspend the vector). Neither the patient, nor the person injecting the liquid will know whether the vial used contains vector or not.

1.39 GTAC considered this proposal at their meeting on 15 December 1999. The Committee deferred their decision subject to the receipt of further pre-clinical data from studies already underway. Final approval was granted in October 2000.

HUMAN IMMUNODEFICIENCY DISEASE

1.40 Human Immunodeficiency Virus (HIV) is the agent responsible for Acquired Immuno Deficiency Syndrome (AIDS). Once infected, the virus replicates and spreads through the immune system. The virus depletes cells, called CD4 T lymphocytes, of the immune system, which are responsible for fighting infections. Such loss of immune system activity exposes those infected to opportunistic infections and tumour proliferation.

1.41 By 2000, it has been estimated that 50 million people worldwide were infected with HIV. It is estimated that 16,000 people throughout the world are infected with HIV each day. Over 90% of these new infections occur in the developing world, especially in sub-Saharan Africa and Asia, where the vast majority of people in these locations have little or no access to effective medical treatment.

1.42 Although Highly-Active Antiretroviral Therapy (HAART) has been relatively successful in treating HIV infection, it is limited by toxicity, the development of resistant forms of virus and has significant side effects. There is, therefore, a need for additional and alternative treatment programmes. Despite innovative prevention efforts, safe and effective HIV preventive and therapeutic vaccines are needed to bring the HIV/AIDS epidemic under control.

A Phase III multicentre trial to test the concept of durable virological suppression in subjects with primary HIV-1 infection or recent seroconversion (GTAC 037). University Hospital of Wales, Brighton Healthcare NHS Trust, Royal Free Hospital NHS Trust, Chelsea and Westminster Hospital.

1.43 This is a multi-national study which will involve about 150 patients with early HIV infection using 'highly active anti-retroviral therapy' (HAART – a cocktail of four drugs). These will be patients who have a consistently low level of virus following treatment with the study drugs after about 12 months. The investigators want to assess whether the immune response to HIV-1 can be stimulated by vaccination, preventing the levels of virus from rising again when the HAART treatment is stopped.

1.44 The two vaccines to be used are ALVAC-HIV and Remune™. Remune™ is a conventional vaccine made from inactivated, modified HIV-1 virus. ALVAC-HIV is a modified canarypox virus which was originally isolated from birds and is asymptomatic in humans. Canarypox vectors have also been used in clinical trials for several other vaccines including rabies and measles. Here the modified virus carries genes for HIV-1 proteins considered likely to promote an immune response. The ALVAC-HIV vaccine has been given to 59 people, including 9 HIV-infected subjects, in other studies and was well-tolerated with no severe adverse reactions. In this study, each patient will receive 18 months of treatment with HAART. They will then be randomised to receive ALVAC-HIV, ALVAC-HIV plus RumuneTM or a placebo control, in addition to HAART treatment.

1.45 GTAC considered this proposal at their meeting in May 2000 and granted the study conditional approval in July 2000.

MALIGNANT MELANOMA

1.46 Primary cutaneous malignant melanoma (skin cancer) has been increasing in prevalence over the past two decades. As awareness has increased more patients have been diagnosed at an early, surgically-curable stage. Over 7,000 patients per year in the US and a similar number in Europe eventually die of the disease if it has spread. Chemotherapy can help alleviate symptoms for patients with advanced disease but a significant overall effect on survival has not been demonstrated for patients with metastatic disease.

A phase I, open label dose escalation trial to assess the safety and immunogenicity of DISC-hGMCSF in patients with metastatic melanoma (GTAC 038). Churchill Hospital, Oxford and Royal Marsden Hospital, London.

1.47 The study concerns patients with advanced melanoma that has spread from the initial site and cannot be removed by surgery. They will be given a genetically modified virus expressing a growth factor involved in the inflammatory response (a cytokine) to see if the normal anti-tumour activity can be enhanced.

1.48 There is evidence that patients can mount an immune response to the disease and there have been some benefits from trials using factors involved in stimulating the immune response, such as interferon.

1.49 A modified herpes simplex virus (HSV; the group of viruses responsible for cold-sores and genital herpes) which has been previously developed for vaccines studies will be injected into a melanoma lesion. This should infect and destroy tumour cells and release tumour antigens for further immune response. It also expresses granulocyte macrophage colony stimulating factor (GMCSF) which is produced by cells in response to inflammation or infection. GMCSF stimulates the growth and activation of white blood cell types that can destroy tumour cells directly or by producing antibodies.

1.50 This is a Phase I dose escalation trial to assess the safety of the material and any local and systemic immune responses or anti-tumour effects.

1.51 This proposal was considered by GTAC at their meeting of May 2000, where it was given conditional approval by the committee. Formal approval was granted in July 2000.

Phase I study of melanoma polyepitope DNA (DNA.Mel3) and melanoma polyepitope modified vaccinia Ankara (MVA.Mel3) in patients with melanoma (GTAC 043). The Churchill Hospital, Oxford.

1.52 This is a study in patients with malignant melanoma where their condition has been treated previously by surgery. There is evidence that these patients can mount an immune response to the disease and there have been some benefits from trials using factors involved in the natural immune response, such as interferon. This study uses vaccination to stimulate an immune response.

1.53 Two vaccines have been prepared for this study, one a DNA vaccine (DNA.Mel3) and the other, a modified vaccinia Ankara (MVA.Mel3). The parental vaccinia vector has a good track record as it was used extensively in a smallpox eradication program. Both vectors have been well tolerated in previous studies using similar vaccines expressing malaria antigens. Each proposed vaccine contains seven melanoma gene sequences which code for proteins which have been shown to induce an immune response in humans.

1.54 The two vaccines will be given to 12 patients with adequately treated stage II-IV melanoma. Six of the patients will receive injections of the MVA vector alone. The remainder will receive injections of plasmid DNA followed by the MVA vector. It is hoped that injection of DNA will cause an initial immune response, which might then be further enhanced by injection of MVA. This procedure is referred to as a "prime-boost" strategy.

1.55 This study was considered by GTAC at their meeting of July 2000, where it was given conditional approval. Final approval was granted in January 2001.

COLORECTAL CANCER

1.56 Colorectal cancer is the second most common cause of cancer-related deaths in the UK. It accounts for 28,000 new cases and 19,000 deaths annually. Surgery offers the only form of curative treatment, but has to be performed before there is tumour spread. The most common site for metastases is in the liver. In a small proportion of patients surgical removal of the liver tumour may be successful but the overall prognosis for the majority of patients with colorectal liver metastases remains poor.

The Safety, Biodistribution and Efficacy of Trovax in Patients with Metastatic Colorectal Cancer (GTAC 039). The Christie Hospital, Manchester.

1.57 The patients to be treated will have advanced cancer of the large bowel which has spread from its initial site. The patients will have previously received surgery and/or chemotherapy and will have either stable disease or disease in remission and will not have

been recommended for further chemotherapy. A protein called the "oncofoetal antigen" or "5T4" is found on the surface of the cancer cells. The investigators aim to immunise patients against 5T4 to alert the immune system to the presence of the cancer cells, hopefully allowing the immune system to target and kill those cancer cells.

1.58 The study drug, designated Trovax, is based on a virus called modified Vaccinia Ankara Virus (MVA) which carries the 5T4 gene. MVA is a member of the family of DNA containing viruses that includes variola (smallpox), cowpox and others. MVA was used safely to inoculate over 120,000 people during the campaign to eradicate smallpox.

1.59 Patients will be injected (into an arm muscle) with a study product. Each will receive 3 injections of Trovax, given at monthly intervals. There will be three dose levels and at each dose there will be groups of four patients. The patients will be followed up for 18 months to assess tolerability, induction of immune responses, biodistribution and response if any.

1.60 This study was considered by GTAC in July 2000 and granted approval in October 2000.

BLADDER CANCER

1.61 Bladder cancer represents the eighth most common cause of cancer death. Although most bladder cancers are superficial, recurrence is very common. It can progress to advanced disease, where despite conventional treatment mortality is approximately 50%.

A Phase I Dose Escalation Trial of ONYX-015, an E1B Attenuated Adenovirus as an Intra-vesical Therapy for Recurrent Superficial/Muscle-Invasive Bladder Cancer (GTAC 040). St. James' University Hospital, Leeds.

1.62 ONYX-015 is a widely used attenuated adenovirus which has a gene deleted (E1B). In many cancer cell types, the normal activity of a protein called p53 is affected. P53 is often referred to as a tumour suppresser gene because its absence causes cells to grow abnormally. The ONYX-015 virus is able to grow very effectively in cells defective in p53 function, but only poorly in normal cells. About 70% of superficial bladder cancers have defects in the p53 tumour suppresser gene.

1.63 The study is a Phase I dose escalation trial to assess the safety of ONYX-015 attenuated adenovirus administered via the bladder. This is a new route of administration for removal of tumours and will be given ascending doses of the vector. Virus will be administered by instillation into the bladder. There is also an option of including a patient due for bladder removal (cystectomy) in each dose level. At the maximum tolerated dose, a total of 9 patients and 3 additional cystectomy patients will be enrolled.

1.64 The proposal was considered by the committee at their meeting in July 2000 and awarded conditional approval in August 2000.

BREAST CANCER

1.65 Breast cancer is the most common cancer in women and the most common cause of death in women between the ages of 35 and 54 years. The 10-year survival rate in patients treated with surgery is about 70%, whereas, in patients whose disease has spread to the lymph nodes (and therefore cannot be completely surgically removed), the 10 year survival falls to 30%. In the year 2000, it is estimated that between 1.1 and 1.4 million new cases will be diagnosed worldwide.

Randomised multi-centre trial evaluating two different vaccination schedules of MVA-MUC-1-IL-2 in women with metastatic breast cancer (GTAC 041). Guy's Hospital, London.

1.66 The goal of this study is to vaccinate patients with a vector, based on vaccinia virus, in the hope of stimulating the patient's own immune system to mount a response that will recognise and destroy breast cancer cells.

1.67 It takes advantage of the fact that in 90% of breast cancers, MUC1 protein is chemically altered and at levels that are higher than in normal cells. This means that in some cancers, such as breast cancer, MUC-1 may "look different" when compared to the protein found in healthy cells. Immune responses to MUC-1 products have been recorded in patients with

advanced breast and ovarian cancer. The study aims to deliver more MUC-1 gene product via the viral vector in the hope of stimulating cells of the immune system to respond to MUC-1-expressing cells.

1.68 Although this protocol was initially reviewed by GTAC for their October 2000 meeting, the submission was later withdrawn.

A phase I/II trial of polyHER2neu polyepitope DNA vaccine encoding HER-2 epitopes in the treatment of epithelial cancers (GTAC 043). St James's University Hospital, Leeds.

1.69 HER-2 (human epidermal growth factor receptor 2) is a receptor overexpressed in a large number of human epithelial tumours, leading to a signal resulting in uncontrolled growth. The vaccine proposed for use in this study is a plasmid containing the genetic codes for eight natural and four modified sequences from the HER-2 gene and is designed to induce an immune response to combat the tumour. This study will include breast cancer patients whose tumours over-express the HER-2 gene and who have the HLA-A2 tissue type required to mount an immune response to the sequences in the vaccine.

1.70 The proposal is for a Phase I ascending dose study in patients with metastatic breast cancer who have failed or cannot tolerate conventional treatment.

1.71 This proposal was considered by GTAC at their meetings of July and October 2000. Although it was rejected, a further resubmission was invited.

CORONARY ARTERY DISEASE

1.72 This is an extremely common disease in the developed world, accounting for one of every 5 deaths in the United States in 1998, with an additional 12,400,000 living victims of angina (chest pain due to coronary heart disease), heart attack and other forms of coronary heart disease.

1.73 Heart muscle needs a plentiful supply of oxygen-rich blood and this is provided through a network of blood vessels via the coronary arteries. Coronary artery disease (CAD) is the end result of atherosclerosis (commonly called "hardening of the arteries"). In CAD, because the blood vessels are narrowed, the heart muscle is deprived of oxygen (called *ischaemia*) and this can lead to tissue damage, angina (typically experienced as chest pain) and, if severe, a heart attack.

1.74 Depending on the location and severity of the problem, some CAD can be treated through a combination of drug therapy and lifestyle changes. In severe cases it may be possible to bypass the blockage by taking a vein from the leg (or the mammary artery from the chest) and connecting it above and below the blockage. This process is known as coronary artery bypass grafting (CABG). This allows blood and oxygen to reach areas of the heart muscle that had been impaired by the blocked flow. For some patients, there are areas of the heart that CABG cannot help, for example where arteries are too small to be amenable to bypass grafting or in areas of very diffuse disease.

A phase I, Randomized, Double-blind, Placebo Controlled, Escalating Dose, Multicentre Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 Gene Transfer Administered by Intramyocardial Injection During Coronary Artery Bypass Grafting (CABG) Surgery in Patients with Incomplete Revascularization (GTAC 047). Oxford Heart Centre, John Radcliffe Hospital.

1.75 An alternative approach would be to try to form new blood vessels in order to increase blood flow; a process termed *therapeutic angiogenesis*. The investigators propose to inject (directly into ischemic heart muscle) an adenoviral vector carrying a gene which should act as a sort of "master-switch" and turn on the production of a set of proteins which favour the formation of new blood vessels and increased blood flow.

1.76 Proteins that act upon the "on/off" switches of genes to regulate the appropriate production of proteins by cells are called *transcription factors*. The transcription factor HIF-1α acts to "switch on" certain genes in human heart cells, specifically when they are deprived of oxygen.

The proteins which these genes encode include an enzyme, the action of which leads to the dilation of blood vessels (to increase blood flow), and certain growth factors which mediate the formation of new blood vessels. In the gene therapy construct to be used HIF-1α has been enhanced by hooking up the part of HIF-1α which provides specificity, to part of a transcription factor from *herpes simplex* (called VP16) which is a powerful driver of gene expression.

1.77 Twenty-eight patients will be recruited (aged 40-79 years) who have CAD that necessitates CABG surgery but who have an area that is found not to be amenable to conventional revascularization. The suitability of the patient for gene therapy will only be definitely determined when confirmed by the surgeon during the CABG operation.

1.78 A small volume of the gene therapy vector or a placebo (made up of the salt and sugar solution which is used to carry the virus) will be injected directly into the heart muscle (intramyocardial injection) at ten sites. The trial will be "blinded" which means that the clinical team will not know whether the patient has received vector or placebo – a list will be held centrally.

1.79 Following surgery the patients will undergo routine monitoring and post-operative care. It is expected that patients will be hospitalised for between 3-7 days. Patients will then return periodically to be assessed for adverse events and potentially evidence of efficacy.

1.80 This proposal was considered by the committee at their meeting in December 2000 and awarded conditional approval. Final approval was granted in May 2001.

X-LINKED SEVERE COMBINED IMMUNODEFICIENCY DISEASE

1.81 X-linked SCID is an inherited disorder that affects boys rendering them extremely susceptible to infections such as bacteria and viruses. These children usually are isolated in sterile environments ("bubble babies") and can also be given drugs to protect against infection whilst waiting for a bone marrow transplant (BMT). If not treated, boys with SCID normally die before they are 1 year old.

1.82 In X-SCID babies, the immune system is not effective because certain types of specialised blood cells (lymphocytes), whose normal function is to fight infections, fail to develop properly. In X-SCID the lymphocytes lack on their cell surface a functional protein (encoded by the (γc gene) which would normally receive signals from molecules called "cytokines". The correct reception and processing of these signals is essential if the cells are to develop properly into fully functional and "mature" lymphoctes.

1.83 Bone marrow transplantation offers a cure for X-SCID and the chances of success are very good (90%+) when a fully matched sibling donor is available. However, only a third of patients have a fully matched donor and the chances of success from other donor sources such as non-related individuals and mismatched parental donors are significantly worse (around 60%). In addition, even where the BMT is successful there may be residual defects of the immune system and detrimental side-effects many years after the transplant.

Phase I clinical gene therapy protocol for X-SCID (GTAC 045). Institute of Child Health, London.

1.84 A recent clinical trial of somatic gene therapy for X-SCID has shown that complete correction of the immunological defects associated with SCID is possible. Data exists to suggest that introduction of the γc gene into lymphoid precursor cells (those destined to mature into lymphocytes), even at a relatively low frequency, could have significant therapeutic benefit, because the cells containing the therapeutic gene appear to have a significant growth advantage.

1.85 The patient's bone marrow will be harvested through a needle placed in the pelvic bones under general anaesthetic. The therapeutic gene will be introduced into cell's derived from the patient's bone marrow using a retroviral vector which has been adapted to facilitate better entry into the target cells and also give improved levels of therapeutic gene expression once integrated. This process will take about 5 days. The cells carrying the new gene will be sorted from those which have not been successfully altered and will be put back into the patient (by infusing them into a vein over about

15 minutes). If after 120 days the procedure has been found to fail, the team will repeat the procedure provided a matched donor has not been identified in the meantime.

1.86 This proposal was considered by the committee at their meeting in December 2000 and awarded conditional approval. Final approval was granted in January 2001.

X-LINKED CHRONIC GRANULOMATOUS DISEASE

1.87 Chronic granulomatous disease (CGD) is a group of rare, inherited disorders of the immune system due to defects in the immune system cells called phagocytes. The defects leave patients vulnerable to severe recurrent bacterial and fungal infections and chronic inflammatory conditions such as gingivitis (swollen inflamed gums), enlarged lymph glands, or tumour-like masses called granulomas.

1.88 In CGD, the granulomas form when white blood cells continue to collect in infected areas even after antibiotics have eliminated the infection. This happens because the defective CGD phagocytes cannot generate the oxygen compounds that normally help shut down the body's immune defences. While not malignant, granulomas can cause serious problems by obstructing passage of food through the oesophagus, stomach and intestines as well as blocking urine flow from the kidneys and bladder.

1.89 Presently, the mainstay of CGD therapy is prompt and aggressive treatment of infections with appropriate antibiotics. In addition, patients are given oral antibiotics prophylactically (as a preventive measure) to reduce the number and severity of infections. CGD can be cured by bone marrow transplant (BMT) if a suitable donor can be found. However, there are significant risks associated with this procedure; the chemotherapy needed prior to BMT is toxic and the transplant itself might also attack the patient's own cells and tissues (a condition known as graft versus host disease).

1.90 Phagocytes (which means "cell eaters") are the white blood cells (also called neutrophils) that circulate in the blood and attack fungal and bacterial invaders. They do so by first engulfing the microbes and then showering them with toxic oxygen compounds. Phagocytes also "clear up" and destroy normal tissue debris in the same way. The phagocytes of X-CGD patients carry a mutation in the gp91-*phox* gene which means that they have a defective version of the enzyme (biochemical catalyst) NADPH-oxidase and are unable to kill certain types of bacteria and fungi.

Phase I clinical gene therapy protocol for X-CGD (GTAC 046). Institute of Child Health, London.

1.91 The investigators propose introducing a functional copy of the gp91-phox gene into cells derived from the patients bone marrow using a retroviral vector. The vector has been adapted such that it should effectively transduce the target cells and also give better levels of therapeutic gene expression once integrated.

1.92 Patients will be injected on 5-6 consecutive days with G-CSF to stimulate bone marrow cells to move into peripheral blood. The bone marrow cells are then harvested from the patient's blood on 2 consecutive days.

1.93 Each patient will be given low dose chemotherapy, to reduce the numbers of the patient's own untransduced bone marrow cells. This is necessary because the transduced cells will have no selective growth advantage and it would not be possible to culture sufficient cells *in vitro* to compete with the non-altered cells in the patient. If the altered cells fail to engraft, the chemotherapy is mild enough to allow for recovery of the patient's bone marrow. Transduced cells will be selected and put back into the patient *via* a vein.

1.94 This proposal was considered by the committee at their meeting in December 2000 and awarded conditional approval. Final approval was granted in January 2001.

METASTATIC CARCINOMA

1.95 After a certain period of time, a primary cancer can spread from the original diseased tissue to other areas of the body via the bloodstream and lymphatic system. In such a case, the cancer is said to have *metastasised* or the patient has *metastatic carcinoma*. Should this occur, the prognosis for the patient is typically poor as the

cancer cells are normally in an advanced state and can have taken up residence in any number of tissues and may be inoperable.

A randomised phase I trial of intravenous CI-1042 (Onyx-015) with or without entanercept in patients with metastatic carcinoma (GTAC 048). Hammersmith Hospital, London

1.96 CI-1042 (previously known as Onyx-015) is a disabled adenovirus which does not grow efficiently in normal cells, but replicates in and lyses (kills by bursting) tumour cells which have a genetic abnormality in the p53 gene (see GTAC 040 for more details). Mutation of the p53 gene occurs in more than 50% of all human cancers. The tumour-killing potential of CI-1042 is dependent upon the tumour cells lacking functional p53. Patients with colorectal and head & neck cancer will be recruited, rather than restricting recruiting to one or the other. Previous clinical trials have demonstrated that CI-1042 was detectable in the majority of head & neck and colorectal patients, whereas other tumours were variably or poorly infected. The study will be restricted to patients with advanced and inoperable tumours that have spread to distant sites around the patient's body.

1.97 CI-1042 has been administered to around 250 cancer patients by intratumoural, intraperitoneal, intra-arterial and intravenous routes. It has also been administered in combination with various chemotherapy regimens. In the UK, the vector has previously been approved by GTAC for several studies involving intratumoural injection.

1.98 Cytokines are messengers (hormone like substances) released by cells which have specific effects on cell-cell interaction, communication and the behaviour of other cells. Tumour necrosis factor (TNF) is a cytokine that has a number of functions. It kills tumour cells (hence its name), is involved in inflammation and has antiviral activity (it is a major mediator of adenovirus clearance). If the anti-viral action of TNF can be suppressed, CI-1042 effectiveness in lysing tumour cells might be increased.

1.99 This study will examine the possibility of enhancing the effect of CI-1042 by "mopping-up" TNF (levels of which will increase following injection of the adenovirus) using a drug called Entanercept. Entanercept is based on the naturally occurring TNF receptor which will bind to TNF blocking its action. Entanercept has been used in tens of thousands of patients to date (for example in the treatment of rheumatoid arthritis) and is well tolerated.

2.00 This study was considered by GTAC at their meeting in December 2000 and granted conditional approval.

SECTION 2: GENE THERAPY REGULATORY ISSUES

GTAC Adenovirus Working Party

2.1 In spring of 1999, GTAC began a review of serious adverse events reporting and issues related to the monitoring of gene therapy patients. As events unfolded in the USA in relation to the death of a patient enrolled for gene therapy in an adenoviral study (See Section 2.11), the GTAC review was concentrated on UK adenovirus studies. At the time of the survey 69 patients, all with advanced cancer, had been recruited into 11 adenoviral gene therapy studies.

2.2 GTAC subsequently agreed to conduct a more detailed review of UK studies and to convene an ad hoc adenovirus working group whose membership would be drawn from GTAC, other regulatory bodies and the research community. One study with approval in the UK which had yet to recruit patients involved the administration of adenovirus via the intra-hepatic artery route. Therefore, the investigator was asked not to recruit into this study until it could be reconsidered in the light of adenovirus working party recommendations.

2.3 The working party met in Spring 2000 and their recommendations have been published in the Sixth Annual Report as supplementary guidance to UK adenoviral gene therapy researchers[6]. The report is also available on the GTAC website (http://www.doh.gov.uk/genetics/gtac/).

New Guidance for Gene Therapy Researchers

2.4 The original GTAC *Guidance to Proposers* was published in 1994[1]. The intervening years have witnessed the evolution of many new technologies related to gene therapy. The New and Emerging Technologies Subgroup (NETS) were asked to review the current status of gene therapy research and to update the guidance to investigators seeking to carry out gene therapy research in the United Kingdom.

2.5 NETS met on 7 April to discuss considerations relating to new technologies and developments in gene therapy. In addition to considering how new technology may affect future gene therapy research, NETS discussed what amendments to GTAC's guidance notes will be necessary to bring the document up to date. These new guidance notes were originally published with our Sixth Annual Report[6] and have been republished with this annual report. They are also available on our website (http://www.doh.gov.uk/genetics/gtac/).

The European Clinical Trials Directive

2.6 Following consensus being reached at the Council of Ministers, the Clinical Trials Directive went before the European Parliament for a number of readings in 2000. The Directive is aimed at ensuring that the conduct of clinical research will be of uniformly high quality and should act to harmonise clinical studies across the European Union.

2.7 After much deliberation in 2000, the Directive was finally published on 1 May 2001. Amongst the many areas of clinical research covered by the document, the Directive requires an Ethics Committee to consider an application to conduct clinical research within 60 days from the date of submission of that proposal. However, committees considering clinical proposals employing gene therapy, xenotransplantation or genetically modified organisms, extensions of 30 days are permitted, with a further 90-day extension period where further consultation is necessary (allowing 180 days in total).

2.8 Member States will have until 1 May 2003 to draw up national legislation implementing the Directive, which must come into force by 1 May 2004.

Cancer Gene Therapy Protocols

2.9 GTAC considered the appropriate level of specificity of patient groups in cancer gene therapy trials. GTAC has previously taken the view studies should be carried out within specific tumour categories. As the field has advanced, it was agreed that it should not necessarily be constrained by precedent, but rather reflect the changing nature of gene therapy research.

2.10 In general, GTAC now considers that, for phase I trials investigating the safety and toxicity of the study product, patients with a range of tumour types can be recruited. However, onsite expertise should be available where there may be a need to accommodate the special implications and risks for certain patient groups. In the case of phase II studies examining efficacy, the patient group should be composed of those with the same type of cancer.

Outcome from a Gene Therapy-related Death in the USA

2.11 In September 1999, the death of a 18-year old study volunteer in a gene therapy research study at the University of Pennsylvania's Institute for Gene Therapy, raised concerns about the safety of adenoviral vectors in gene therapy, especially when administered to blood supply of the liver[6]. The patient had an inherited disorder where his liver was unable to break down ammonia, called Ornithine Transcarbamylase Deficiency (OTC). The study involved delivering an adenoviral vector carrying the OTC gene into the patient's liver by way of direct injection into the hepatic artery. The purpose of the study was to determine the maximum safe dose and the patient received the highest scheduled dose. The procedure went uneventfully but over the following 4 days the patient's condition deteriorated rapidly and he died.

2.12 US researchers submitted all relevant data for consideration by the Recombinant DNA Advisory Committee (RAC) at their meeting on 8-10 December 1999. The meeting revealed that the team at the Pennsylvania Institute may have seriously breached regulatory protocol. The death further raised concerns about potential under-reporting of adverse events to the regulatory authorities and the oversight of gene therapy clinical trials in the USA. The Recombinant Advisory Committee (RAC) three-day meeting took place just weeks after President Clinton requested that the RAC and the FDA (the Food and Drug Administration) determine how patients could be better protected in gene therapy trials. Senator Bill Frist held the first of a series of hearings on gene therapy oversight.

2.13 While there is no conclusive answer as to why the patient died, University of Pennsylvania researchers and others believe the patient experienced an extreme immune reaction, most likely to the vector, perhaps combined with a parvo-virus infection and malfunctioning liver.

2.14 As a consequence, clinical trials at the Institute where the death took place have essentially ground to a halt. The incident also served to highlight the importance of reporting adverse events and reactions of patients during clinical research and of paying close attention to writing accurate, meaningful information for participating patients. The death reinforced the role of ethics committee review of clinical research and the strict adherence to the clinical protocol, as approved by that committee.

SECTION 3: INTERNATIONAL DEVELOPMENTS IN GENE THERAPY

FRANCE:

Gene Therapy of Severe Combined Immunodeficiencies

3.1 Dr. Alain Fischer and colleagues at the Necker Hospital in Paris reported, in the journal *Science*, the first clinical successes in gene therapy research in 2000. They treated children with Severe Combined Immunodeficiency (otherwise known as "bubble boys") using an experimental gene therapy vector. The process restored sufficient function to the patients' immune system to enable them to return home from hospital.

3.2 By using defective retroviral vectors, relatively high efficiency gene transfer into hematopoietic progenitors (found in the blood) can safely be achieved ex vivo, in the presence of cytokines such as FLT-3L, SCF, MGDF and of a fibronectin fragment. Following *in vitro* studies and *ex vivo* work in a mouse model, researchers set up a clinical trial for the X-linked form of severe combined immunodeficiency (SCID) caused by mutations of the γc gene. Five patients were enrolled. Selected CD34(+) cells from patients' marrow were *ex vivo* infected then re-infused. No adverse effects occurred with a follow-up of almost 2 years. In four patients, a complete correction of T cell immunodeficiency was achieved which is so far sustained. Patients can therefore live normally without any form of treatment.

3.3 These results provide a proof of principle for the efficacy of gene therapy based on the selective advantage provided to transduced cells. Assessment of long-term results will be required in order to determine how long the effect will persist. Extension of this form of treatment for closely related inherited disorders of the immune system can be anticipated.

THE UNITED STATES:

Gene Transfer for Haemophilia

3.4 Mark Kay at Stanford University, Katherine High at the Children's Hospital in Philidelphia and colleagues reported encouraging results in the treatment of haemophilipia B, a clotting disease where a protein called Faxtor IX is defective. They have been working to establish an experimental basis for a gene transfer approach to treating the disease.

3.5 Using an adeno-associated viral vector (AAV) expressing Factor IX introduced into skeletal muscle, they have shown in haemophilic mice and dogs that long-term expression of clotting factor can be achieved at levels that would result in an improvement in clinical symptoms of the disease.

3.6 A phase I trial intramuscular injection of AAV-delivered Factor IX has been initiated to evaluate the safety of this procedure in patients with severe haemophilia. To date, eight subjects have been enrolled at three doses. There has been no evidence of local or systemic toxicity in any of the subjects, including no evidence for inhibitor formation or for inadvertent germline transmission of vector sequences. Muscle biopsies have shown unequivocal evidence of gene transfer and expression by PCR, Southern blot, and immunohistochemistry. Some subjects have shown evidence of circulating Factor IX levels above baseline, >1% but <2%, and have had concomitant decreases in clotting factor usage. In additional pre-clinical studies, administration of an AAV vector into the portal vein of haemophilic dogs has resulted in considerably higher circulating levels of Factor IX, on the order of 5-14%, whereas delivery to skeletal muscle never resulted in levels higher than 1-2% in haemophilic dogs.

3.7 A proposed clinical trial of AAV-mediated, liver-directed gene transfer for haemophilia B is now underway. AAV-mediated gene transfer is a promising approach to the treatment of haemophilia B.

SECTION 4: RESULTS FROM SELECTED UK GENE THERAPY TRIALS

4.1 For its next Annual Report, GTAC will include a comprehensive list of outcomes from gene therapy clinical trials conducted in the UK thus far. GTAC will be inviting researchers to submit their reports over the next years. As a prelude, a small selection of GTAC-approved trials is described below.

GTAC 02, 07 & 08: Gene Therapy for Cystic Fibrosis

4.2 Cystic fibrosis (CF) is one of the most common, serious genetic diseases in the UK. Gene therapy is considered as a possible treatment for CF lung disease, which is the major cause of mortality in CF individuals. In these studies, a non-viral gene transfer vector, in which plasmid DNA is complexed with cationic liposomes, has been employed.

4.3 Two double-blinded clinical studies, each involving 12 CF patients, in which a gene transfer formulation was administered to the nasal epithelium have been completed by the research group. The studies aimed to test the safety and efficacy of single and multiple doses. The results showed no evidence of inflammation, toxicity or an immune response towards the DNA/liposomes or the CF protein. Nasal epithelial cells were collected after each of three doses for a series of efficacy assays to measure vector DNA and mRNA, CFTR protein, bacterial adherence, and halide efflux *ex vivo*. Airway ion transport was also assessed *in vivo* throughout the studies.

4.4 In the first single-dose study, gene transfer was detected in six of the eight treated patients, although the gene transfer was modest and transient, indicating that repeated administration is likely to be required for long-term gene expression. The results showed that DNA/liposomes could be successfully re-administered to the nasal epithelium without apparent loss of efficacy.

4.5 In conclusion, these studies and others have demonstrated proof of principle for CF gene therapy. Current research is now focused on improving the efficiency and duration of CF gene transfer in the lung.

GTAC 018: Gene Therapy for Glioblastoma

4.6 Two Phase I clinical trials have been carried out in patients with malignant brain tumours using HSV 1716, a modified version of Herpes Simplex Virus (or the virus that causes cold sores). The virus has been modified so that it is unable replicate in normal cells, but in actively dividing cells, such as cancer cells, it can multiply and kill the cell.

4.7 Study 1 was designed to demonstrate the 'proof of principle' that HSV 1716 could be injected directly intratumourally in patients with recurrent glioblastoma in doses that, from animal studies, are likely to produce an antitumour effect. Nine patients were recruited. All demonstrated active malignant glioma at biopsy immediately before injection. The majority were heavily immunocompromised. All but one had antibodies against herpes virus (i.e. were seropositive for HSV). There were 7 glioblastomas, one anaplastic astrocytoma and one oligodendroglioma. HSV 1716 was injected directly into the recurrent tumours using a multi-point injection technique (up to 10 injections per patient). Doses of 10^3 to 10^5 plaque forming units were used. Patients were intensively followed for 6 days as inpatients with daily clinical analysis, haematological, biochemical, immunological and radiological investigations. They were followed thereafter as outpatients until the present time or to death.

4.8 Study 2 was designed to demonstrate the proof of principle that HSV 1716 was capable of infective replication when injected intratumourally into patients with glioblastoma but remained a safe procedure. Twelve patients were injected with HSV 1716. All proceeded to tumour resection and 11 have received further anticancer treatment post operatively. There were 11 glioblastomas and one anaplastic astrocytoma. Six patients were measurably immunocompromised. 10 were seropositive, two seronegative for HSV. Patients were injected intratumourally with 10^5pfu of HSV 1716 and followed post operatively as in study 1. Between 5 and 9 days later the tumours were excised and submitted to viral analysis. Post operatively patients were treated with either

chemotherapy or radiation therapy. Safety and radiological data were collected lifelong or to the present.

4.9 None of the 21 patients at any time showed any clinical or radiological evidence of toxicity due to intratumoural injection of HSV 1716. Two of three seronegative patients developed antibodies to HSV. The toxicity of post-operative treatment in patients following injection with HSV 1716 was no greater than expected in uninjected patients. Evidence of HSV 1716 replication in tumour tissue has been obtained in the majority of the patients in the second study. Three patients in study 1 and eight patients in study 2 remained alive at times up to 40 months following treatment with HSV 1716.

4.10 From these studies it has been concluded that HSV 1716 can be given safely as an intratumoural injection to patients with newly diagnosed or recurrent malignant glioma. This safety is demonstrated in patients who seroconvert, who show evidence of intratumoural HSV 1716 proliferation and in patients undergoing immunosuppressive therapy with steroids, chemotherapy and radiotherapy. No patient has suffered HSV treatment related toxicity. The demonstration of HSV 1716 proliferation in tumour tissue gives hope that it may be used in the treatment of patients with brain tumours.

4.11 A third study is underway in which the virus HSV 1716 is injected into the brain cavity after resection of the tumour. The patients then proceed to treatment with either chemo or radiotherapy. This study is designed to demonstrate the safety of HSV 1716 when injected directly into brain rather than tumour and to develop methods of response assessment for use in later studies. So far eight patients have been enrolled into the study without evidence of toxicity from HSV 1716.

SECTION 5: REFERENCES

[1] Gene Therapy Advisory Committee: First Annual Report January 1994-December 1994. Health Departments of the United Kingdom. London. Department of Health. 1995.

[2] Gene Therapy Advisory Committee: Second Annual Report January 1995-December 1995. Health Departments of the United Kingdom. London. Department of Health. 1996.

[3] Gene Therapy Advisory Committee: Third Annual Report January 1996-December 1996. Health Departments of the United Kingdom. London. Department of Health. 1997.

[4] Gene Therapy Advisory Committee: Fourth Annual Report January 1997-December 1997. Health Departments of the United Kingdom. London. Department of Health. 1998.

[5] Gene Therapy Advisory Committee: Fifth Annual Report January 1998-December 1998. Health Departments of the United Kingdom. London. Department of Health. 1999.

[6] Gene Therapy Advisory Committee: Sixth Annual Report January 1999-December 1999. Health Departments of the United Kingdom. London. Department of Health. 2000.

SECTION 6: GLOSSARY

AAV
Adeno-associated virus.

Adenovirus/adenoviral
A DNA virus, usually associated with mild upper respiratory tract infections.

DNA (deoxyribonucleic acid)
The chemical (nucleic acid) substance in chromosomes and genes in which genetic information is coded.

Chemotherapy
Treatment with chemicals that destroy cancerous tissue.

Cell
The smallest unit of living organisms. It has been estimated that the body of a human adult comprises 50 million, million cells.

Cytotoxicity
The property of being able to kill cells directly.

Ex vivo
"Outside of the body." Sometimes cells can be taken out of the patient and treated externally. Once treated, they can be returned to the patient's body.

Gene
Genes are the biological units of heredity – a sequence of DNA which codes for *protein*. It has been estimated that the human genome comprises up to 65,000-75,000 genes.

Genetic disease or disorder
Conditions which are due to defects in the genetic constitution of an individual. They may be the direct consequences of defects in single genes; or in whole chromosomes, parts of which may be lost, duplicated or misplaced; or due to the interaction of multiple genes.

Germline cell
Cells in embryonic life that become sperm in males and eggs in females and transmit genetic information to the next generation.

Herpes simplex
The virus responsible for causing cold-sores.

HSV
Herpes simplex virus – a retrovirus.

Immune response
A specific white blood cell or antibody response to an antigen (protein).

Immunohistochemistry
A diagnostic test used to determine whether a particular protein is present or not.

Immunomodulation
The use of a drug to alter, suppress of strengthen the body's immune system.

In vitro
Experiments conducted outside of living organisms, such as in cell culture (literally "in glass").

In vivo
When experiments are performed in living organisms.

Intraperitoneal
Within the cavity that contains the abdominal organs.

In Utero
In the womb (uterus).

LREC
Local Research Ethics Committee.

MREC
Multi-centre Research Ethics Committee.

Malignant
Cells that have lost their normal control mechanisms and develop into a cancer.

Metastatic, metastases
Cancer which has spread from the site of the original tumour to other tissues/organs in the body.

PCR
Polymerase Chain Reaction. A highly sensitive test used to diagnose the presence of specific stretches of DNA.

PIL
Patient Information Leaflet.

Placebo
A dummy treatment compared to which an experimental treatment must produce better results in order to be considered effective.

Prodrug
Relatively inert compounds that can be converted to an active or toxic form.

Promoter
A short piece of DNA contiguous with a gene which controls whether or not (and at what rate) the corresponding *protein* is produced.

Protein
Proteins are essential constituents of the body that are coded for by DNA. They form the structural materials of muscles, tissues, organs, and are regulators of function, as enzymes/hormones.

Proto-oncogene
Genes which play a role in cell division. There is evidence to suggest that certain cancers are caused by activation (switching on) of these genes.

Retrovirus/retroviral vector
A type of virus used in gene therapy as a vector. Such viruses are usually animal viruses rather than agents of human disease. They are made inert so that they can enter a human cell carrying a gene for gene therapy without causing disease.

Somatic Cell
The cells which make up the body of an individual excluding the egg or sperm cells.

Southern Blotting
A diagnositc test used to determine whether a specific piece of DNA is present or not.

Stem Cell
A cell that can self renew and produce all the types of cells.

Tumour regression
A cancer that has become smaller or has completely disappeared.

Tumour suppressor gene
Such genes produce proteins to regulate the rate at which cells divide. The absence or dysfunction of a tumour suppressor gene is associated with the production of cancer cells.

Unresectable
Unable to be fully removed by surgery.

Vaccinia
A member of the family of DNA-containing viruses which also includes smallpox virus. It was the standard vaccine against smallpox.

Vector
A carrier, usually a virus or lipid, to transport foreign DNA across the cell membrane into the cell.

Virus
A protein covered DNA or RNA containing organism which is only capable of reproducing within the host cell. Some viruses cause disease, such as chickenpox or influenza. Viruses suitably modified can be used as means of delivering a gene into cells.

Guidance on making proposals to conduct Gene Therapy Research on human subjects.

PART 2

SECTION 1: GENE THERAPY RESEARCH ON HUMAN SUBJECTS

Introduction

1. This document gives guidance on the procedures that should be followed in the United Kingdom when proposals are made to conduct gene therapy research on human subjects. It details the information that should be submitted in order to enable the Gene Therapy Advisory Committee (GTAC) to assess the acceptability of gene therapy research proposals.

2. Some guidance is also given on the requirements of other regulatory bodies or committees, including Local Research Ethics Committees, the Medicines Control Agency, the Health and Safety Executive and the Department of Environment, Transport and the Regions.

3. The guidance should be read in addition to general guidance on clinical trials and research governance in the NHS (see Further Reading).

4. Supplementary guidance and reports have been issued by GTAC in relation to monitoring of patients enrolled in adenoviral gene therapy studies and in utero gene therapy. Both can be obtained as stand-alone documents from the GTAC web-pages. (www.doh.gov.uk/genetics/gtac.htm).

GTAC review process

5. GTAC reviews proposals to conduct gene therapy research and provides advice in related areas. GTAC reviews are in addition to those of local research ethics committees (LREC), whose roles and responsibilities are unchanged.

6. GTAC approval should be obtained before NHS personnel conduct any gene therapy research on human subjects, whether conducted on NHS or other premises, in the UK. GTAC approval should also be sought where any part of gene therapy research on human subjects takes place in the UK. This would include enrolment, monitoring, follow-up and other study related procedures. NHS personnel who conduct gene therapy research overseas are encouraged to submit protocols to GTAC for information (this should include any information that will be given to prospective participants).

7. GTAC expects applicants to provide a full account of what is proposed. This should place particular emphasis on the ethical aspects, including an assessment of the scientific merit and safety of the proposed work.

8. In conducting such reviews, GTAC continues to reflect the principles established by the Clothier committee, namely that:

- gene therapy is research and not innovative treatment;
- only somatic therapy should be considered. Germ line interventions are considered to pose unacceptable safety and ethical concerns;
- patients should take part in gene therapy research trials only after a full explanation of the procedures, risks and benefits and after they have given their informed consent, if they are capable of doing so; and
- therapeutic research involving patients must not put them at disproportionate risk. For this reason gene therapy should be restricted to patients with serious disorders where current alternative treatments are not wholly effective.

Definition of gene therapy

9. GTAC has reviewed and revised the 1994 definition of gene therapy in the light of experience and of definitions established by other countries and international bodies. GTAC wishes to maintain a wide definition of gene therapy in order not to exclude certain novel approaches from GTAC oversight. Within the context of GTAC's terms of reference, gene therapy can be defined as:

> The deliberate introduction of genetic material into human somatic cells for therapeutic, prophylactic or diagnostic purposes.

10. This definition is intended to include studies involving the use of most of the established techniques for delivering genes into cells. A non-exhaustive list of examples includes genetically modified viral vectors, liposome-encapsulated DNA, anti-sense techniques, naked DNA injection, DNA-mismatch repair, GM stem cell therapy, and xenotransplantation of animal cells (but not solid organs).

11. GTAC does not normally wish to consider any study which may be deemed to fall within the general definition, but which is adequately reviewed by other national or local ethics committees. Such research includes, for example:

- transplantation or transfusion of organs or cells, from whatever human source, provided that they have not been genetically modified;
- xenotransplantation of solid animal organs;
- vaccine studies, involving the use of genetically attenuated viruses intended to raise a prophylactic immune response to that virus (provided that the virus does not express any heterologous proteins);
- ex vivo fusion of autologous cells and other cells, for example dendritic cells, for the treatment of cancer.

12. In cases of doubt, researchers are invited to contact the GTAC Secretariat for an informal discussion prior to submitting a research proposal.

Germ line gene therapy

13. In line with the Clothier committee report and relevant international Instruments, research aimed at modifying the germline of subjects will not be considered at this stage. The possibility of inadvertent targeting or modification of germ cells should be carefully assessed during pre-clinical studies. GTAC will need to be satisfied that measures are in place to ensure that patients do not conceive a child during or shortly after the study.

Relationship between GTAC and other agencies

Local Research Ethics Committees

14. Any proposal to carry out gene therapy research on human subjects must comply with the established system of review by a local research ethics committee (LREC). LRECs must be consulted about any research proposal involving NHS patients, their records or NHS premises. A new web-site containing details of LRECs will be launched shortly: http://www.doh.gov.uk/research/recs.

15. Where a research project is to be carried out within five or more LRECs' geographical boundaries and hence would normally be referred to a multi-centre research ethics committee (MREC), GTAC acts as the MREC for gene therapy research.

16. The timing of LREC reviews will vary depending on the local arrangements and on the nature of the research. Researchers are advised for reasons of practicality to submit applications to GTAC in advance of the LREC.

Medicines Control Agency

17. The MCA is required by legislation to assess the safety and quality of medicinal products to be used in clinical trials. Before testing gene therapy products in patients, sponsors or investigators must apply to the Medicines Control Agency for a Clinical Trial Certificate (CTC), a Clinical Trial Exemption (CTX), or a Doctors and Dentists Exemption (DDX), or claim the "named-patient" exemption in writing.

18. Further details of MCA's role in regulating gene therapy medicinal products can by obtained by contacting the MCA Clinical Trials Unit (Tel: 020 7273 0327) and be found at: www.open.gov.uk/mca

Medical Devices Agency

19. Some forms of gene therapy may involve the use of medical devices, for example novel delivery systems. Details of the regulation of medical devices and the role of the MDA can be found at: http://www.medical-devices.gov.uk/

UK Xenotransplantation Regulatory Authority (UKXIRA).

20. UKXIRA is responsible for approving proposals to conduct xenotransplantation on human subjects. If a gene therapy proposal involves the transfer of viable animal tissue to patients, the GTAC Secretariat will discuss with the UKXIRA Secretariat how to consider the application. In some cases UKXIRA will consider a proposal in parallel with GTAC. UKXIRA's main interest will be confined to any additional elements that relate to the xenotransplant. Further information can be found at: http://www.doh.gov.uk/ukxira.htm

Genetically Modified Organisms Regulations.

21. Proposals to conduct gene therapy research, where they involve the use of live genetically modified organisms (for example, a genetically modified viral vector delivery system), must comply with the relevant regulations controlling the contained use or deliberate release of genetically modified organisms. These are concerned with the protection of human health and the environment. Contained use is where control measures are used to limit contact of the GMOs with people and the environment. Where contact cannot be appropriately limited the activity is likely to constitute a deliberate release.

22. Further details on contained use legislation may be found in, "A guide to the Genetically Modified Organisms (Contained Use) Regulations 1992", as amended in 1996 (ISBN 0-7176-1186-8). This Guide will be replaced by "A guide to Genetically Modified Organisms (Contained Use) Regulations 2000" once expected new legislation has been produced (ISBN 0-7176-1758-0). Detailed technical guidance in matters such as risk assessment and containment measures can be found in the Advisory Committee on Genetic Modification's Compendium of Guidance which is available on the HSE web site: http://www.hse.gov.uk/ .

23. For further advice about contained use legislation and technical guidance contact the Health and Safety Executive, GM Notifications Unit, Technology Division 6, Magdalen House, Stanley Precinct, Bootle, Merseyside, L20 3QZ. Tel: 0151 951 4722, Fax: 0151 951 3474.

24. For further details on deliberate release legislation contact the Department of Environment, Food and Rural Affairs: http://www.defra.gov.uk/

Method of working

25. In order to develop experience of the issues raised by gene therapy, GTAC has previously sought comments from external reviewers and held discussions with the proposers in full committee. However, increasing experience of gene therapy proposals allows a case-by-case approach to the review process.

26. GTAC therefore has moved towards a more graded system of review, based on the novelty and complexity of the proposal and the extent to which it clearly falls within GTAC's remit.

27. In general, full GTAC review will be appropriate for studies that involve novel delivery systems, that extend the use of known agents to a different disease, raise new ethical issues, pose significant risks to subject's health or raise wider safety issues for the patient, staff or public health or are proposed by groups with no prior experience of clinical gene therapy research.

28. In all cases it is recommended that those contemplating gene therapy research submit a completed GTAC application form at an early stage. The Secretariat will then be in a position to provide informal advice on the need for a full GTAC application and the likely route of review.

Decisions of the committee

29. The outcome of the above review process will be sent to the lead applicant, the LREC, the host institution and the MCA. This might take the form of unconditional approval; conditional approval; deferral with recommendations for changes before the proposal is reconsidered or rejection. In all cases where further information is sought, the Committee will give its reasons to the applicants in writing and encourage dialogue via the Secretariat.

Disclosure of information

30. Applications to GTAC will be considered to be in confidence and treated as such throughout the review process, including the external review stage. However, care should be taken to ensure that information that might serve to identify individual patients or groups of patients is not included. This is particularly relevant to studies that involve rare diseases or small patient groups.

31. Some elements of a proposal may be considered to be commercially confidential. Such information should be clearly marked and supported by a reasoned justification for the claim. This will enable the Secretariat to determine how to handle the proposal during review. It should be stressed that failure to provide sufficient information at the initial stages will inevitably lead to delay in the GTAC review process.

32. A summary of the discussions at GTAC is placed in the public domain after each meeting. This is normally via a summary of the meeting posted to the GTAC web pages (www.doh.gov.uk/genetics/gtac.htm).

Reporting requirements

Adverse Event Reporting

33. Researchers are required by law to report all serious unexpected adverse reactions[12] (SARs) in gene therapy studies to the MCA in accordance with their requirements. In addition all serious adverse events[13] (SAE) should be reported to GTAC within 14 days (7 for death) regardless of whether the event is deemed related or unrelated to the gene therapy and whether unexpected or expected. In the case of a subject's death, a more detailed report, including, where appropriate, findings at post mortem, additional studies and a statement on the cause of death should be submitted as soon as possible.

34. Summaries of all Adverse Events should be reported to GTAC on an annual basis as part of the annual progress report (see paragraph 40). Adverse events should also be notified to the relevant LREC in accordance with their requirements.

35. The report should use the standard format for reporting adverse reactions to medicinal products, however GTAC's reporting arrangements are in addition to those for reporting severe adverse reactions to the MCA.

Long term flagging project

36. GTAC has advised that there should be arrangements for the long-term monitoring of the subject and for monitoring any subsequent children born to those who have taken part in gene therapy research. This will in future be possible via the GTAC Flagging Project involving the NHS Central Registry and the Office of National Statistics (for those living in England and Wales) or the General Register Office for Scotland (for those living in Scotland). This study has been approved by an independent MREC.

37. Proposers are asked to seek informed consent from all subjects capable of giving it (or otherwise on behalf of the subject) at the time of their enrolment for monitoring of their long-term health and on behalf of any children that the patient may conceive following participation in the study.

38. For the purposes of clinical audit, subject's NHS records will be flagged indicating that they have taken part in a gene therapy research study. Investigators will be asked to provide directly to the Office for National Statistics (or General Register Office for Scotland) the NHS numbers of each subject along with a cipher specific to the study and one to identify the subject within that study. Submissions to the ONS will be on a six-monthly basis using the supplied electronic pro-forma for the purpose of emailing returns.

39. Clinical records and specimens from gene therapy patients should be stored indefinitely to enable follow-up. The storage of DNA samples needs special consideration and appropriate consent.

Progress reports

40. All investigators with active studies will be asked to provide an annual progress report to GTAC. A format for this will be supplied by the Secretariat each year, covering matters such as progress with the recruitment of subjects, observed adverse events and any relevant

clinical findings. These progress reports will not be released by GTAC, however, the data provided, for example on the total number of gene therapy patients, may be incorporated into the GTAC annual report. No information will be released that may identify individual patients.

41. GTAC also expect to see reports on completion of the study and would encourage prompt publication in peer-reviewed journals as a means of promoting wider dissemination of research findings.

Information to be included in GTAC applications

GTAC must be given sufficient information to make a judgement about the ethical acceptability of the study.

Proposals for gene therapy research submitted to GTAC should normally consist of:

- ✔ A GTAC application form;
- ✔ The clinical protocol;
- ✔ Patient information material and consent forms;
- ✔ Information about relevant qualifications and experience of the principal investigator(s);
- ✔ Details supporting the suitability of the research centre;
- ✔ Supporting technical appendices.

42. GTAC has developed and application form to provide a common framework for an overview of the design of the study and the issues that it raises. The application form is available on the web, by email from the Secretariat or as a hard copy.

43. For full proposals, the clinical protocol and a succinct summary of relevant pre-clinical and safety data (possibly including that prepared for other regulatory bodies) should support the application form.

44. Proposers should aim to strike a balance between giving sufficient information to enable the committee and external referees to understand the study whilst keeping the documents accessible to the lay members of the committee.

45. The following headings are suggested to structure the proposal. In some cases the information may be adequately conveyed in the study protocol, in others it may be necessary to provide additional supporting information in the application form or technical appendices.

A. Objectives and rationale

46. There should be a brief introductory statement that provides the background to the proposed research. It should refer to the disease to which the study relates, its prevalence, severity and health burden; their natural history and biology; the available therapies, what is to be learnt from the research and the potential for improving the subject's health.

B. Patient population

47. The proposal should describe and justify the proposed study population, bearing in mind GTAC's key principles (paragraph 0).

Risk/benefit

48. The proposal should include an appraisal of the risks to the subject and the possible benefits. This should include a summary of the alterations to normal clinical care that will arise as part of the research, especially any invasive procedures and those that may be uncomfortable or inconvenient for the subject (such as procedures that involve lengthy or frequent attendance as outpatients or in-patients or requirements to remain in an isolation room).

49. The patient's disease should also be relatively stable with a predictable likely clinical progression. In cases where there is rapid progression, GTAC will need to be convinced that the clinical management of the patient will not be impaired by the requirements of the trial.

C. The gene construct and delivery system

50. The proposal must include details of the genetic material and its manufacture to enable an assessment of the safety and likely benefit. Technical information such as sequence data, derivation of vectors and producer cell lines may be provided as part of the supporting technical appendices.

51. The proposal should describe the nature and structure of the genetic material that is to be administered and the rationale for its use. It should include:

- an overview of the therapeutic gene construct and its regulatory elements;
- the methods used to produce it, including any producer cell lines;
- the method of delivery, and;
- the form in which the material will be administered to the patient.

Manufacture

52. The proposal should summarise the arrangements for the manufacture and handling of the therapeutic product. The detailed arrangements for achieving compliance with the requirements of the MCA are not normally required, but may be appended as part of the supporting technical material.

D. Prior studies

53. The proposal should describe the evidence relating to the safety and likely efficacy of the proposed gene construct and delivery system. Wherever possible the data presented should relate to the proposed construct and delivery system in the most appropriate *in vitro* or animal model of the disease. Where this is not possible there must be a full account of how the data is extrapolated to the intended disease and construct. In some cases available data may also be extrapolated to avoid excessive animal studies, especially in non-human primates.

54. The proposal should provide a reasoned justification for the choice of construct and delivery system. In particular, GTAC will be looking for evidence that the safety of the proposed study has been considered in depth at the pre-clinical and clinical stages. This should include consideration of the stability of safety features in any viral vectors used and tests to assess the presence of contaminants.

55. Where possible, reference should be made to any previous applications to GTAC, to published studies and to guidance from GTAC or others on the safety and tolerance of the vector system in human subjects.

Pre-clinical studies

56. The evidence provided from pre-clinical studies should normally include:

- Studies of the gene delivery system;
- Studies demonstrating gene transfer and expression and biological effect;
- Studies to demonstrate target specificity;
- Studies relating to the route of entry;
- Studies related to the safety of the genetic material and the delivery system. In some cases this may be supported by material elsewhere in the proposal, such as on the delivery system and manufacture.

Distribution to non-target organs

57. The proposal should provide evidence of the target specificity of the therapeutic product and, where appropriate, the absence of accumulation / retention on non-target tissues or organs, especially the gonads.

Previous clinical experience

58. A summary of relevant data from previous clinical trials, including peer-reviewed publications, should be submitted to support the safety and likely efficacy of the proposed study.

E. Study protocol

59. The detailed arrangements for the clinical and technical procedures involved in the research should be specified in the study protocol. This

should include an outline of the clinical procedures and the tests used to monitor the patient.

Study design

60. The type of study being proposed, the size of the study population and other relevant factors should be detailed. There should be some consideration of whether the procedures and requirements are reasonable and equitable.

Criteria for inclusion/exclusion

61. The inclusion and eligibility criteria should be detailed. The number of subjects should be given, along with a comment on the likelihood of recruiting sufficient subjects. There must be careful characterisation of the specific patient population for the studies regarding not only their disease, its stage, and previous standard treatments, but also the expected prognosis.

62. The proposal should set out what other options would be available to such patients in clinical practice or current clinical research. Specific inclusion and exclusion criteria by virtue of disease, abnormal tests or treatment, should be justified explicitly in relation to the treatment and/or its evaluation.

63. Where subjects are to be HIV tested for the purpose of excluding HIV positive patients from the gene therapy study, consent for the test should be explicitly sought and the appropriate provision made for counselling.

64. The eligibility criteria should take account of the need to minimise the risk of unintended transfer of genetic material to germ cells or the fetus. If conception is possible, it should normally be a condition that subjects or their partners use an effective form of birth control during and for at least 3 months after the study. Fertile women should have a negative pregnancy test shortly before commencing the study.

65. Children should be the subject of research only when it is essential and the information could not be obtained from adult subjects or in any other way. Where children are to be the subjects of such research, then the presumption must normally be that there is some possibility of therapeutic benefit for the child. The child's parents or legal guardian must be fully informed and consent obtained. The minimum age for entry into an adult trials should be set at 18 years

Dose escalation studies

66. Particular attention should be given to the design of dose escalation studies to ensure that early indications of dose limiting toxicity can be identified. Investigators should set the initial dose to be administered to patients at least two logs lower than the maximum safe dose predicted by pre-clinical studies.

67. GTAC will normally wish to see details of the arrangement for assessing toxicity and considering progression to the next dose level. This might include details of the parameters to be used in assessing adverse effects and toxicity. Where there is a reference to standard criteria, e.g. the NCIC toxicity criteria, it is not necessary to reproduce these in full.

68. For certain protocols raising particular safety issues, GTAC may wish to be provided with safety data for each dose level before giving permission to proceed to a higher dose. A case-by-case assessment will be made by GTAC when reviewing proposals to determine whether investigators should seek approval for progression between doses. No unnecessary delay in granting approval for to proceed to the next dose level is anticipated.

69. In any Phase I study, no further patients should be dosed following an unexpected, clinically meaningful grade IV toxicity until the investigator has adequately reviewed the monitoring and safety data. Procedures for review in this event should be detailed in the protocol. Any necessary amendments to the protocol and patient information material should be approved by GTAC before the trial recommences.

Additional clinical procedures

70. The protocol should detail the clinical procedures, particularly those that are in addition to or differ from normal patient care. This should include details of any preliminary treatments, for example surgery or chemotherapy to remove or reduce the number of abnormal cells.

71. The procedures and regime for administering the gene therapy material should be given, including the nature and timing of administration and monitoring.

72. If cells are to be removed and treated *ex-vivo* details should be provided of the type of cells and the procedures to be used.

Monitoring

73. Screening tests used solely for the purpose of the study should be explained and justified. Arrangements should be set out for explaining to patients, and performing those that are not part of standard care, but which result from participation in the study.

74. The arrangements for monitoring subjects before and after the administration of the genetic material should be given. It should specify the frequency and duration of monitoring, the biochemical, physiological, pathological tests to be done, the clinical endpoints of the study and whether special post-mortem studies will be requested if a patient dies.

75. The monitoring procedures should be designed with a view to identifying at an early stage the possible side effects so that action can be taken to prevent or mitigate such events. The relevance of tests used in monitoring the study should be set out, together with sufficient detail on those that are not standard practice to enable their assessment. The way in which such tests are to be analysed in relation to study end-point should be made clear, including the validation of novel techniques where appropriate. If material is to be stored and/or transported long distances, evidence should be provided to show that the process of storage and/or transport and any consequential delay, do not adversely or unpredictably affect the results obtained.

76. There should also be some consideration of the methods used to determine whether the gene sequences are inserted and expressed in the subjects. This might include, where available, tests to determine any non-target effects, such as expression in other tissues or cells or shedding of vector into the wider environment.

77. A reference sample of the material injected should be stored to allow for retrospective analysis. Where possible, it is also recommended that serum (and, if feasible, cell) samples should be taken at suitable intervals and stored to provide for retrospective analysis in the event of adverse reactions.

78. GTAC has prepared separate guidance on monitoring of studies involving adenovirus vectors (see Part Two: Section Two).

F. Information for patients and consent

Patient Information Leaflets

79. The application should detail the arrangements for informing prospective subjects, or their parents or guardians in the case of children, about the research before seeking consent to take part in the study. The application to GTAC will need to include copies of the patient information sheet that subjects will receive, as well as any wider promotional material about the research team or unit (including any material available on the Internet) if this mentions gene therapy.

80. There should be a simple introductory document that explains, in non-technical language, what is proposed. This should be supported by arrangements for further oral and/or written information. Advice on preparing clear patient information material is at Annex 1.

81. GTAC is sensitive to the hopes and motives of potential participants who have a life-threatening disease, and it is imperative that they understand clearly when a trial offers them no prospect of clinical benefit. It is also important to make clear whether or not participation in the initial non-therapeutic stages of a research programme influences their eligibility for future therapeutic studies.

82. GTAC also advocates appropriate independent counselling for research subjects, and details of the arrangements should be clear from the proposal and the patient information leaflet.

Consent

83. Research subjects should take part in gene therapy research trials only after a full explanation of the procedures, risks and benefits and after they have given their consent, if they are capable of doing so.

84. Consent should also be sought for each participant's NHS number, in an anonymised form, to be sent to GTAC and to be recorded on the central NHS register. In order to obtain consent to the flagging arrangements, two standard paragraphs should be inserted into the patient information leaflet (see Annex 1).

Insurance

85. The proposal should confirm that appropriate insurance or indemnities are in place to cover the participants in the trial.

Payments

86. Subjects should have their travel and other out of pocket expenses fully reimbursed. The patient information sheet should make clear that they will not be expected to meet the costs of any clinical procedures (material, tests or medical care) related to the study.

G. Details of Investigator(s) and nature of the research site

87. GTAC wishes to be satisfied that gene therapy is only conducted in centres of excellence, until it can be considered to be a normal part of clinical research. Therefore, the proposal should provide details of the staff (especially the Principal Investigator) and the facilities in which the research will take place (the Host Institution). In particular this information should demonstrate that there is:

- a substantial multidisciplinary team of clinical researchers,
- a suitable infrastructure of facilities in clinical and laboratory environments,
- on-site support in a range of disciplines, including microbiology/infection control, immunology, and;
- a proven track record of high-grade clinical research.

88. The proposal should be supported by a summary of the relevant training and experience (in the form of a brief CV) of the principal investigator (PI). The names and qualifications of junior clinical and research staff should also be provided. There should be appropriate arrangements to ensure adequate supervision of junior staff and access for the patients to the PI in the event of problems or queries.

89. Arrangements should be in place to ensure that there is no untoward conflict of interest, financial or otherwise, between the trial sponsor and those individuals responsible for enrolling and caring for the patients.

90. It is strongly recommended that the proposal identifies an individual with day-to-day responsibility for overall co-ordination, including liaison with GTAC. This might not be the same person as the PI, recognising that such people are often involved in a number of trials and other activities.

Containment

91. The arrangements to safeguard people other than the research subject, including clinical and non-clinical staff, relatives and visitors and the wider public will normally form part of requirements of the Health and Safety Executive. The GTAC proposal should, however, include information on the anticipated hazards of the proposed research and the proposed control measures. In particular it should highlight any measures over and above those required for normal clinical care, such as keeping the subject in isolation during the study, handling of any dressing and any restrictions on visitors.

ANNEX 1 – WRITING INFORMATION LEAFLETS FOR THOSE PARTICIPATING IN GENE THERAPY RESEARCH

92. The following section is based on guidance first issued in 1995. It provides more detailed advice for those with clinical responsibility for participants and those with responsibility for the design of gene therapy trials.

93. This guidance should be read with the sources of general advice on patient information and consent (see Bibliography)

Informing Patients

94. Enabling the potential subjects of research to make a decision whether or not they might participate is one of the most important aspects of the ethical acceptability of research. They must be well informed about the procedures and risks of the protocol and the responsibilities that they are being asked to take on. This is true of all medical research which involves human subjects, but is especially so in the field of gene therapy. Not only is the topic unusually complex, but there is likely to be a need for long term follow up.

95. Although information can be given in a number of ways, the written information leaflet is particularly important and should always be provided. It is a permanent record of the key points of any research trial, to which the patient can refer, and therefore a critical element in informing consent. The document also provides a source of reference for families and friends. In addition it gives both Local Research Ethics Committees (LREC's) and GTAC an opportunity to assess this aspect of the research protocol.

General Principles

96. There is no single correct way of writing information for patients. The aim must be to present sufficient but not excessive information in a form that is understandable. This calls for thoughtful and tested use of language, vocabulary and presentational techniques.

97. Understanding, and recall, of what to many patients will seem to be complex information, are reduced by:

- anxiety
- poor presentation
- complex language, technical terms and jargon.

98. Conversely, understanding and recall are enhanced by:

- keeping the format simple, so that it can be read and re-read at leisure;
- use of plain English;
- ensuring that other modes of communication, such as counselling, reinforce and amplify the written information, but do not contradict it.

99. Patients must be encouraged to ask questions about the research. Time must be set aside for the investigator to go over the information with patients to ensure that they understand all the implications. Patients will often only remember important questions after the first counselling.

100. The advice contained in this guidance covers three aspects of preparing information leaflets:

- The information to be included
- How to present the information
- How to evaluate its effectiveness

What to Include

101. It is important to anticipate common concerns. Below are listed some common questions.

- Why have I been chosen for the study?
- Is the treatment really likely to cure me or not? The answer should be unambiguous. There should be no false hope.
- Are there any risks or disadvantages for me?

- What will the treatment entail? How, when, where and how often will it be administered and monitored?
- What will the side effects be? Will it be painful or uncomfortable?
- What costs or inconveniences may I incur?
- What are the responsibilities placed upon me for follow-up?
- What will the trial help to demonstrate?
- What action should be taken if I become unwell?
- Who can I talk to about this study?

102. The following points should be covered in addressing these concerns.

Why the research programme is being undertaken

103. Explain the purpose of the study. This needs to cover:

a. The research questions being asked:

- Why are they important?
- How might they be answered?
- Why has gene manipulation been chosen?
- How the study has been designed:
- Increasing dosage. Why is this necessary?
- Use of placebo controls and what this means.
- Does the study involve more than one centre?
- Evaluation of results.

b. The implications of the research for the individual.

Research procedures

104. Describe and explain the procedure(s) and commitment of participants in terms of time, costs, and how data will be collected (such as blood tests, x-rays, interviews). Describe any restrictions the research might place on the patient, particularly the use of isolation rooms and restrictions on visiting.

Consequences of participating

105. The predictable consequences of participating in the study should be explained.

a. State whether or not there are possible benefits of participating in the proposed study. For research trials which are not reasonably expected to provide a therapeutic benefit to participating patients the information leaflet should clearly state that no direct clinical benefit is expected to occur as a result of participation in the study, although knowledge may be gained that may benefit others.

b. Describe the nature and likelihood of risks, pain, injury or other harm, that may occur.

c. Where it is appropriate to the patient, describe alternative therapies, including those being assessed in other research trials.

Non-participation or withdrawal from the study

106. Emphasise that participation in any study is voluntary. The decision to take part or not, should not influence any present or future treatment or care. Patients should know that they can withdraw from the study at any time without having to give a reason for doing so. Draw attention to any additional risks that might be associated with an incomplete course of treatment.

Use of contraception

107. It is important to avoid the possibility that any of the reagents used in gene transfer research could harm a foetus. Advise women that they should not become pregnant before or during the course of their participation in the study. Inform both men and women when effective contraception or abstinence is required during

the active phase of their participation in the study and also for at least 3 months afterwards. Depending upon the nature of the research trial the information sheet might advise any woman not to participate if she thinks she may wish to become pregnant.

Confidentiality/ Privacy

108. Affirm that confidentiality of personal information of trial participants will be protected. State who might have access to their anonymised research records and why this is necessary. In trials where personalised data needs to be reviewed, the patient's agreement must be obtained and this aspect of the research should be clearly explored in the information leaflet.

Long term follow-up

109. It is important to evaluate the long term safety and efficacy of gene transfer. This requires co-operation of participants in follow-up beyond the active phase of the study. Explain the need for this commitment from the outset. The information leaflet or consent form should include a list of persons who can be contacted during the follow-up period.

110. Patients participating in gene therapy studies will be subject to clinical audit via the NHS central records system. In addition they will be invited to participate in the GTAC Flagging Project involving the NHS Central Registry and the Office of National Statistics. Proposers are asked to seek informed consent from all subjects at the time of their enrolment for monitoring of their long-term health and on behalf of any children that the patient may conceive following participation in the study.

111. The following paragraphs should be inserted into the patient information leaflet:

"Gene Therapy is a new development. Every effort is made to be sure it is safe but we need to watch out for any unexpected effects. To make this possible, all people who have gene therapy are flagged by the NHS records system. Accordingly, your NHS number and details of the trial in which you are participating will be provided to the Department of Health (DH) so that your participation in this trial can be recorded on the National Health Service Central Register. This information will be used for purposes of long-term follow-up. You will not be contacted by DH directly but your GP may be asked to provide information on your health on occasion.

In theory, gene therapy could affect the next generation. To cover this possibility, any children born to a person who had gene therapy will be flagged also and followed through until they are 16 years old. This system is subject to the same protection of confidentiality as all medical records. Any studies of these medical records will be under the supervision of the Gene Therapy Advisory Committee of the Department of Health who will make sure confidentiality is respected."

Further support

112. The information leaflet should make clear to potential participants who can be approached for

a. further information

b. counselling.

How to write it

113. Experience has shown that it is best to:

- keep sentences short
- make only one point in each sentence
- use simple words
- avoid technical terms whenever possible. When they cannot be avoided, explain what the terms mean in simple language
- repeat important points in different ways
- avoid crowding pages with too much information
- summarise the key points.

Evaluation of a Patient Information Leaflet

114. To determine how well an information leaflet will be understood it needs to be evaluated. Asking people not acquainted with the area to read the leaflet is the best way. They might include

Reading ease	Verbal description	Typical text	Estimated Percentage who would understand
90-100	Very easy	Comics	97
80-90	Easy	Tabloids	95
70-80	Fairly easy	Popular	90
60-70	Standard	Magazine	90
50-60	Fairly hard	Broadsheet	77
30-50	Difficult	Academic	31
0-30	Very hard	Scientific	7

administrative or clerical staff in the hospital, or non-medical friends. The management of your hospital may be able to assist in "piloting" the leaflet. Patient groups and other voluntary organisations are an important source of advice on both design and piloting leaflets.

115. The two most common ways in which written information is evaluated formally involve using readability formulae and through formal assessments by patients.

116. The "readability" of any text can be estimated by the application of standard formulae. Most modern word processing software can derive these figures automatically. The table above gives an interpretation of the Flesch reading ease score. A reading ease score for patient information leaflets of between 80 and 90 is desirable.

117. Assessments of leaflets by patients might include measures of understanding and satisfaction with the information provided.

Special Issues

118. Potential subjects need time to make a decision about their participation in the research. They should have an opportunity to consider the information provided, seek further information and to consult with a named independent counsellor.

119. Where the study involves children who are not capable of giving consent, an information sheet for parents or guardians should be prepared according to the principles above. In addition, information should be provided to the child which is appropriate to the understanding ability of that child.

120. Additional consideration should be given to the needs and requirements of subjects whose first language is not English. The importance of written information is often greater in such circumstances. Special care should be taken to have information leaflets in other languages checked for accuracy, and to ensure cultural and ethnic sensitivities are properly handled.

121. Every effort should also be made to ensure that individuals who have difficulty reading are not disadvantaged through lack of information.

Further reading

1 NHS Management Executive. "A guide to consent for examination or treatment" 1990 Department of Health. This is currently being updated.

2 Scottish Office "A guide to consent for examination or treatment" Scottish Office Home And Health Department.

3 Royal College of Physicians. "Research involving patients". London: Royal College of Physicians. 1990.

4 Consumers for Ethics In Research. "Spreading the word on research or patient information: how can we get it better?" CERES. 1993 (This is a very practical guide to drafting patient information with excellent examples on both good and bad practice. This can Be obtained from: CERES, PO Box 1365, London N16 0BW).

5 Flesch, R. (1948) "A new readability yardstick." Journal of Applied Psychology 32: 221-33.]

SECTION 2: REPORT OF THE ADENOVIRUS WORKING PARTY

INTRODUCTION

1. The Gene Therapy Advisory Committee (GTAC), established by Government in 1993, oversees the conduct of gene therapy in the United Kingdom. GTAC approval must be obtained before somatic gene therapy or gene transfer research is conducted on human subjects. The primary concern of GTAC is the ethical acceptability of each research proposal and GTAC review places emphasis on the need to ensure the safety of the subjects of research.

2. This document is intended as a supplement to the GTAC's General Guidance Notes15, and should be consulted when proposals are made to conduct adenoviral gene therapy in the United Kingdom.

BACKGROUND

3. In Spring 1999 GTAC began a review of serious adverse events (SAEs) reporting and issues related to the monitoring of gene therapy patients. As events unfolded in the USA in relation to the death of a patient enrolled for Gene Therapy in an adenoviral study, the GTAC review was concentrated on UK adenovirus studies. At the time of the initial survey, 69 patients, all with advanced cancer, had been recruited into 11 adenoviral gene therapy research protocols.

4. GTAC subsequently agreed to conduct a more detailed review of UK studies and to convene an ad hoc adenovirus working group whose membership was drawn from the GTAC, other regulatory bodies and the research community. The latter survey confirmed that no major or life-threatening toxicity had occurred in relation to the use of adenoviruses in the UK.

5. The working group met in London, on 11 April 2000 with the following remit:

   - To review current UK practice in adenoviral gene therapy clinical trials, including adverse event reporting.
   - To establish recommendations in relation to GTAC's guidance with respect to adenoviral gene therapy clinical trials.

6. The following supplement to GTAC's Guidance Notes is issued in accordance with the recommendations of the Working Party and approved by GTAC. The recommendations are based on such factual information as received regarding the adenovirus-related death of the patient in the USA. Specific recommendations on monitoring reflect these considerations, and suggest practicable and generally available measures to address these. The need to issue further recommendations, in the light of receipt of substantive additional information will be kept under review.

SUMMARY OF MAIN CONCLUSIONS AND RECOMMENDATIONS OF THE WORKING PARTY.

Patient surveillance and monitoring

7. The level of monitoring recommended by the working party reflects concerns related to risks associated with the route of administration, particularly those related to systemic exposure to the vector.

8. In addition, for dose escalation studies, it is recommended that patients be closely monitored for early signs of toxicity. Such signs, which may not be severe, may indicate that the dose levels are approaching a maximum tolerated dose under which circumstances investigators should reduce the increments between future doses.

9. Clinical monitoring that is part of routine monitoring (e.g.: blood pressure, temperature, respiratory rate and so on) should be carried out at least quarter-hourly for the first hour, hourly till 6 hours, then six hourly for 24-48 hours. In addition to routine monitoring the following additional investigations are recommended as a minimum:

   - Measurement of anti-adenovirus antibody, both pre- and post-dosing.
   - Pre-treatment assessment of T cell population – CD3/CD4/CD8. Whether or not conducted prospectively, it is recommended that samples be stored to

allow for retrospective analysis in the event of a serious adverse reaction.

Further, the storage of serum (and, if possible, cell) samples at suitable intervals (including pre-administration) is strongly encouraged to provide for retrospective analysis in the event of adverse reactions. Where possible, a reference sample of the material injected should be stored to allow for retrospective analysis.

10. For intra-vascular administration, it is recommended that investigators routinely measure (with rapid turn-around for results) the following investigations, as close as practicable to the start of treatment and daily in the first 3-4 days post-treatment, and longer if they show abnormalities:

- Full blood count with white cell and platelet counts (6-8 hourly for the first 24 hours).
- C-Reactive Protein (6-8 hourly for the first 24 hours).
- Complement C3 and, if possible, C3 breakdown products
- Coagulation studies
- Fibrinogen
- Fibrin split products
- Liver enzymes: AST/ALT/ALP
- Gamma Glutamyl Transpeptidase (GGT)
- Bilirubin
- Creatinine, Urea & Electrolytes
- Urine microscopy
- Proteinuria

The working party further recommend that researchers consider monitoring:

- Serum cytokines (eg IL-6/IL-10/TNF-α).

11. Whether or not conducted prospectively, it is recommended that serum be stored to allow for retrospective analysis in the case of severe adverse reactions.

12. The results of pre-treatment assessments should be known **before** treatment commences.

Intra-hepatic Arterial Administration

13. Administration of adenovirus by the intra-hepatic artery route was considered to present a greater theoretical risk to the patient than the intra-tumoural route. Additional considerations will be applied by GTAC in reviewing studies utilising this route. The committee will need to be satisfied that use of the intra-hepatic arterial route is fully justified.

14. Researchers proposing to administer adenovirus by the intra-hepatic artery route should implement extensive patient monitoring and this should be performed on an in-patient basis. GTAC will require reassurance that all patient monitoring data and safety data has been considered, prior to progression to the next dose level in dose escalation studies.

Standardisation of Dose

15. The need for accurate standardisation of dose was acknowledged. The working party recognised that this was a global issue and would seek to encourage the research community to work towards the development of reference standards for use as controls in assays of vector potency. Until a universal standard has been established, researchers should endeavour to attain comparability in terms of infectious units: particle ratios in any given study or series of studies.

16. Investigators should set the initial dose to be administered to patients at least two logs lower than the maximum safe dose predicted by pre-clinical evaluation of the actual vector to be used by the specific route of administration. If one patient out of three experiences a grade III/IV toxicity at any dose level it is recommended that the cohort be expanded to 6 in order to establish whether the maximum tolerated dose has been reached.

17. For certain protocols raising specific issues, GTAC may wish to be provided with safety data for each dose level before giving permission to proceed to a higher dose. A case by case assessment will be made by GTAC when reviewing proposals to determine whether investigators should seek approval for

progression between doses. No unnecessary delay in granting approval to proceed to the next dose level is anticipated.

18. Whilst GTAC approval may be initially granted for half or whole log increments, investigators are encouraged to reduce these increments at high doses, where patient monitoring is predictive of marked toxicity at the next planned dose. GTAC approval should be sought for any change to dose escalation increments and the relevant patient monitoring data submitted for consideration.

19. No further patients should be dosed in an ongoing study following an unexpected, clinically meaningful grade IV toxicity until the monitoring and safety data have been adequately reviewed by the investigator. Suitable amendments to the protocol, designed to minimise risk to future patients and to inform patients of any additional risks, should be submitted to and approved by GTAC before the trial recommences.

Appropriateness of Patient Group

20. To date, all patients enrolled in UK adenoviral gene therapy clinical trials have had advanced cancers. Whilst the choice of patient group should reflect the stage of the investigation, a case by case assessment will be carried out by GTAC with regard to patient group suitability. In reaching a decision, GTAC will carefully consider the potential risks against the possible benefits. It is recommended that only patients whose disease is severe or life-threatening should be recruited into dose escalation studies.

21. The patient's disease should also be relatively stable with a predictable likely clinical progression. In cases where there is rapid progression of the disease, GTAC will need to be convinced that the clinical management of the patient will not be impaired by the requirements of the trial.

Reporting of Serious Adverse Events & Reactions

22. A serious adverse event or drug reaction is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

23. Researchers are required by law to report all serious unexpected adverse reactions (SAR[16]) in gene therapy studies to the MCA in accordance with their regulations. In addition (in accordance with GTAC's requirements for all gene therapy studies) any serious adverse event (SAE[17]), expected or unexpected and whether deemed related to the study product or not, should be reported to GTAC within 14 days (7 days for death). Summaries of adverse events should be reported to GTAC on an annual basis. SAEs should be notified to the relevant LREC in accordance with their requirements.

24. Investigators are strongly encouraged to include in their annual reports to GTAC any monitoring data which is suggestive of a dose-related toxicity but which do not result in clinical adverse events in patients. Such data might assist in the design of future studies by other researchers.

25. In addition, GTAC would value notification of SAEs in studies conducted outside the UK, which may have implications for the safety of patients enrolled in UK studies.

Public Awareness and Sharing of Information

26. A key recommendation of the working party was that any data considered by GTAC to be relevant to patient safety should be provided to other UK adenoviral gene therapy researchers, thereby permitting informed amendment of existing studies. Such sharing of information will be by agreement with the submitting investigator and will have all proprietary or confidential information erased.

WORKING PARTY MEMBERSHIP

- Professor Alisdair M Breckenridge,
  Chair of Committee on Safety of Medicines
- Dr Brian Davis, Medicines Control Agency.
- Professor Anthony Dayan*,
  Emeritus Professor of Toxicology,
  University of London
- Dr Martin Gore†, The Royal Marsden.
- Dr Peter Harris, Cobra Therapeutics.
- Professor Stanley Kaye†,
  CRC Department of Medical Oncology,
  The Beatson.
- Dr Paul Logan, Health & Safety Executive
- Professor Pedro Lowenstein†,
  University of Manchester.
- Dr Vivien Mautner, University of Birmingham
- Professor Norman C Nevin*
  (Chairman) Department of
  Medical Genetics Belfast City Hospital
- Professor Anthony Pinching*,
  St Bartholomew's and the Royal London School
  of Medicine and Dentistry,
  Queen Mary & Westfield College.
- Dr Peter Searle,
  CRC Institute for Cancer Studies, Birmingham
- Dr R Spiegel, Sr V P Medical Affairs,
  Chief Medical Officer,
  Schering Plough Research Institute.
- Professor C Michael Steel*
  School of Biological & Medical Sciences,
  University of St Andrews
- Dr Lincoln Tsang, Medicines Control Agency.

*GTAC Members.
†Not present at the meeting on 11 April.

ANNEX A – GTAC TERMS OF REFERENCE

The terms of reference of the Gene Therapy Advisory Committee (GTAC) are:

(1) To consider and advise on the acceptability of proposals for gene therapy research on human subjects, on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks;

(2) To work with other agencies which have responsibilities in this field including local research ethics committees and agencies which have statutory responsibilities – the Medicines Control Agency, the Health and Safety Executive, and the Department of the Environment;

(3) To provide advice to UK Health Ministers on developments in gene therapy research and their implications.

The Committee will have a responsibility for:

(a) Providing advice for applicants on:

(i) The content of proposals, including the details of protocols, for gene therapy research on human subjects;

(ii) The design and conduct of the research;

(iii) The facilities necessary for the proper conduct of the research;

(iv) The arrangements necessary for long term surveillance and follow up.

(b) Receiving proposals from doctors who wish to conduct gene therapy research on human subjects, and making an assessment of:

(i) The clinical status of the subjects;

(ii) The scientific quality of the proposal;

(iii) The scientific requirements and technical competence necessary for carrying out gene therapy research effectively and safely;

(iv) Whether the clinical course of the particular disorder is known sufficiently well for the outcomes of therapy to be assessable;

(v) Sound information, counseling and advice to be given to the subject (or those acting on behalf of the subject);

(vi) The potential benefits and risks for the subject of what is proposed.

ANNEX B – MEMBERSHIP OF GTAC

Chairman

Professor Norman C Nevin BSc, MD, FFPHM, FRCPath. FRCPEd, FRCP
Queen's University Belfast and
Belfast City Hospital

Members

Professor David Harrison BSc, MD, FRCPath, FRCP (Ed)
Department of Pathology,
University of Edinburgh

Mrs Rosemary Barnes
Chief Executive
Cystic Fibrosis Trust
Kent

Professor Ian Hart BVSC, MRCVS, PhD, FRCPath
United Medical & Dentistry Schools
of Guy's and St Thomas' Hospitals
London

Mrs Ann Hunt
Tuberous Sclerosis Association

Professor James Neil BSc, PhD, FRSE
University of Glasgow Veterinary School

Professor Anthony Pinching DPhil, FRCP
St Bartholomew's and The Royal London
School of Medicine & Dentistry
Queen Mary & Westfield College
London

Mrs Irene Train RGN, RM, RHV, QIDN
Formerly Director Public Health Nursing
Clwyd Health Authority

Mr Michael Harrison
Chambers of Peter Andrews QC, London

Dr Sohala Rastan, PhD
SmithKline Beecham Pharmaceuticals/Ceros.

Ms Caroline Benjamin RN, MSc
MacMillan Genetic Associate
Liverpool Women's Hospital Trust

Dr. David Crosby OBE, FRCS, LL.M
Retired Surgeon, South Glamorgan

Professor Alex Markham, PhD
Molecular Medicine Unit, St James's Hospital,
Leeds

Reverend Dr. Lee Rayfield SOSc
Vicar, Maidenhead

Dr Andrew Lever FRCP, FRCP(Ed), FRCP Path, F. Med. Sci.
Department of Medicine,
University of Cambridge

Observers

Department of Health:
Dr Elaine Gadd

Medicines Control Agency:
Dr Elaine Godfrey
Dr Brian Davis
Dr Lincoln Tsang

Secretariat

Mrs Margaret Straughan
Dr Jayne Spink
Mrs Beryl Keeley
Dr Mark Bale
Dr John Connolly

ANNEX C – REGISTER OF MEMBERS INTERESTS

GTAC members have declared the following personal share holdings or funding from the biotechnology/pharmaceutical industry.

Professor Norman C Nevin	None
Professor David Harrison	None
Reverend Dr. Lee Rayfield	None
Professor Alex Markham	Scientific Advisory Board Member, Oxagen Ltd. Director, Molecular Solutions Ltd.
Dr. Andrew Lever	None
Dr. David Crosby	None
Mrs Rosemary Barnes	Director, Association of Medical Research Charity Non-Executive, Director, Greenwich healthcare Trust, Non-Executive Director, Greenwich Building Society (now Portman Building Society)
Professor Ian Hart	None
Mrs Ann Hunt	None
Professor James Neil	Research grant from Intervet International BV Ad hoc consultancy, Q-One Biotech
Professor Anthony Pinching	Infrequent consultancies with Roche, Pharmacia Upjohn, Glaxo Wellcome. Travel Sponsorship from Boehringer Ingelheim and Glaxo Wellcome.
Mrs Irene Train	None
Mr Michael Harrison	None
Dr Sohala Rastan	Employee of Smithkline Beecham Pharmaceuticals. Holder of Smithkline Beecham shares & share options. Founder of Ceros.
Ms Caroline Benjamin	None

ANNEX D – EXTERNAL EXPERT ADVISERS TO GTAC

Professor John Arrand,
Paterson Institute for Cancer Research,
Manchester.

Professor Jon Austyn,
John Radcliffe Hospital, University of Oxford.

Sir Roy Calne, University of Cambridge.

Professor James Carmichael,
University of Nottingham.

Dr Keith Channon,
The John Radcliffe Hospital, Oxford.

Professor Judith M. Chessells,
Institute of Child Health, London.

Dr Jean-Marc Collombert,
Imperial School of Medicine, London.

Professor Cotter,
St Bartholomew's & Royal London
School of Medicine.

Professor Alan Craft,
Royal Victoria Infirmary, Newcastle Upon Tyne.

Professor David Crossman,
Northern General Hospital, Sheffield.

Professor A. Dalgleish,
St. George's Hospital Medical School, London.

Professor Kay Davies,
University of Oxford.

Professor J Geroge Dickson,
Royal Holloway College, University of London.

Professor John A Dodge, CBE,
Dept of Child Health,
Singleton Hospital, Swansea.

Professor M Dowsett,
The Royal Marsden NHS Trust,
Fulham Road, London.

Professor John Goldman,
Imperial College of Medicine,
Hammersmith Hospital, London.

Professor Farzin Farzaneh,
The Rayne Institute, London.

Professor John Goldman,
Imperial College of Medicine,
Hammersmith Hospital, London.

Dr R Gopal,
Public Health Laboratory Services, Colindale.

Professor Robert Hawkins,
Christie CRC Research Centre, Manchester.

Dr Tim Helliwell,
University of Liverpool.

Dr Simon J Hollingsworth,
The Royal Free & University College London
Medical School.

Dr S Howie,
Dept of Pathology, University of Edinburgh.

Dr Charles Lacey,
Imperial College School of Medicine, London.

Dr JA Ledermann,
The Royal Free & University College London
Medical School.

Professor Nick Lemoine,
ICSM at Hammersmith Hospital, London.

Professor R Leonnard,
ICRF Medical Oncology Unit, Edinburgh.

Dr Keith N Leppard,
University of Warwick, Coventry.

Professor P Lowenstein,
University of Manchester.

Professor D Lowrie,
National Institute of Medical Research.

Dr Michael Marber,
The Rayne Institute, St. Thomas' Hospital,
London.

Dr David Miles,
Guy's Hospital, London.

Professor AC Minson,
University of Cambridge.

Professor Neil McIntyre,
Royal Free Hospital, London.

Dr David Mutimer,
The Queen Elizabeth Hospital, Birmingham.

Dr Nikolai V Naoumov,
University College London.

Professor ES Newlands,
Imperial College of Science,
Technology & Medicine, London.

Professor Peter O'Hare,
Marie Curie Research Center, Surrey.

Professor M Partridge,
Kings College Hospital, London.

Dr G Poston,
Royal Liverpool Hospital.

Dr CM Preston,
MRC Virology Unit, Glasgow.

Professor MA Richards,
St. Thomas's Hospital, London.

Dr S Shaunak,
Hammersmith Hospital, London.

Dr M Stanley,
Dept of Pathology, University of Cambridge.

Dr Peter Searle,
CRC Institute of Cancer Studies, Birmingham.

Professor Robert Souhami,
Royal Free & University College Medical
School, London.

Dr Richard Thompson,
King's College Hospital, London.

Dr Adrian Thrasher,
Institute of Child Health, London.

Professor RA Weiss,
Wincleyer Institute for Medical Sciences,
London.

Professor CR Wolf,
University of Dundee.

Professor Wynford-Thomas,
University of Wales College of Medicine,
Cardiff.

ANNEX E*: SUMMARY OF UK GENE THERAPY RESEARCH 1993-2001

GTAC No.	Protocol Title	Details	Centre	Outline Approval	Trial Started	Vector	Gene	Packaging cell line	No. of patients
001	Adenosine deaminase gene transfer in a child with severe combined immunodeficiency syndrome	SCID-ADA	Institute of Child Health/ Great Ormond Street Hospital	JAN 93	MAR 93 CLOSED	Retro-virus	ADA	pOAM-P1	1
002	Gene Therapy Research for Cystic Fibrosis	CF Nasal trial	Royal Brompton Hospital	MAR 93	SEP 93 CLOSED	Liposome	CFTR	–	15
003	A pilot study of idiotypic vaccination for follicular B-cell lymphoma using a genetic approach	B-cell lymphoma	MRC Cambridge	JUL 93	NOV 94 CLOSED	Plasmid	anti-idiotype immuno-globulin	–	7
004	Use of gene transfer to determine the role of tumour cells in bone marrow used for autologous transplantation and the efficiency of immunomagnetic "purging" the bone marrow	Neuroblastoma	ICRF Bristol	FEB 94	Trial WITH-DRAWN	Retro-virus	LNL-6/neo G1N-neo	PA317	–
005	Gene Therapy for metastatic melanoma: Assessment of expression of DNA constructs directly injected into metastases	Metastatic melanoma	ICRF Oxford	MAY 94	JUN 95 CLOSED	Plasmid	IL-2	–	13
006	The treatment of metastatic malignant melanoma with autologous melanoma cells that have been genetically engineered to secret IL-2	Metastatic melanoma	Institute of Cancer Research/ Royal Marsden Hospital	FEB 94	OCT 94 CLOSED	Retro-virus	IL-2	GP+env AM12	12
007	Towards gene therapy for cystic fibrosis	CF Nasal trial	Oxford/ Cambridge	FEB 94	MAY 95 CLOSED	Liposome	CFTR	–	12
008	Gene Therapy Research for Cystic Fibrosis	CF Nasal trial	Edinburgh	MAY 94	6.95	Liposome	CFTR	–	16

GTAC No.	Protocol Title	Details	Centre	Outline Approval	Trial Started	Vector	Gene	Packaging cell line	No. of patients
009	Gene Therapy Research for Cystic Fibrosis	CF Lung trial	Royal Brompton Hospital	SEPT 94		Liposome	CFTR	–	–
010	Transfer of the Human Multi-drug Resistance Gene into the Haemopoietic Cells of Patients Undergoing High Dose Therapy and Autologous Stem Cell Transplantation for Malignant Lymphoma	Lymphoma	University College London Medical School	DEC 94	OCT 95 CLOSED	Retro-virus	MDR-1	AMI2M1	3
011	Genetic prodrug activation therapy for breast cancer	Breast Cancer	Hammersmith Hospital	OCT 95	OCT 95 CLOSED	Plasmid	Cytosine deaminase	–	12
012	Use of a recombinant vaccinia virus for therapy of cervical cancer	Cervical Carcinoma	University of Wales, Cardiff	JUN 95	SEP 95	Vaccinia	TA-HPV	–	1+8
012A	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat Cervical intraepithelial neoplasia III	Cervical intraepithelial neoplasia III	University of Wales, Cardiff	MAY 96	SEP 96 CLOSED	Vaccinia virus	HPV E6 and E7	MRC-5	12 CLOSED
012B	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat Cervical intraepithelial neoplasia III	Cervical intraepithelial neoplasia III	University of Wales, Cardiff/ University of Manchester	AUG 97	JAN 98 CLOSED	Vaccinia virus	HPV E6 and E7	–	8
012C	Use of recombinant Vaccinia vaccine (TA-HPV) to treat Vulval intraepithelial neoplasia III	Vulval Intraepithelial Neoplasia III	St Mary's Hospital, Manchester	JAN 00	FEB 00	Vaccinia virus	HPV E6 and E7	MRC-5	18
012 D	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat Ano-genital intraepithelial neoplasia III	Ano-genital intraepithelial neoplasia III	Addenbrooke's Hospital, Cambridge	APR 00	JUN 00	Vaccinia virus	HPV E6 and E7	MRC-5	12

GTAC No.	Protocol Title	Details	Centre	Outline Approval	Trial Started	Vector	Gene	Packaging cell line	No. of patients
013	A proposal to study the efficacy of transplantation of autologous retroviral transduced bonemarrow in patients homozygous for the W402X mutation (Hurlers syndrome)	Hurlers Syndrome	Royal Manchester Children's Hospital, Manchester	DEC 95	MAY 97 CLOSED		pLX	GP+env AM12	3
014	Phase I, Open-Label, Dose-Escalation Trial of Intra-Tumoral Injection with an E1B Attenuated Adenovirus ONYX-015, into Recurrent and Locally Advanced p53(-) Squamous Cell Tumours of the Head and Neck	Head and Neck Cancer	Beatson Oncology Centre, Glasgow	JAN 96	MAR 96 CLOSED	Adeno-virus	E1B deleted	Human embryonic Kidney cell line 293	30
014A	A phase II trial of intravenous cisplatin, 5-FU and intratumoral injection with ONYX-015 into recurrent, chemotherapy naive squamous cell tumours of the head and neck	Head and Neck Cancer Phase II Study	Beatson Oncology Centre, Glasgow	JUL 97	JUL 97 CLOSED	Adeno-virus	E1B deleted	Human embryonic Kidney cell line 293	30
014B	Phase I, Open-Label, Dose-Escalation Trial of Intraperitoneal Injection with an E1B Attenuated Adenovirus in patients with recurrent/ refractory ovarian carcinomas	Recurrent/ refractory ovarian cancer	Beatson Oncology Centre, Glasgow	FEB 97	MAR 97	Adeno-virus	E1B deleted	–	12
015	Towards gene therapy for Cystic Fibrosis	CF Nasal Trial	Oxford/ Cambridge/ Leeds/ Manchester Consortium	MAY 96	JUL 96	Liposome	CFTR	–	11

GTAC No.	Protocol Title	Details	Centre	Outline Approval	Trial Started	Vector	Gene	Packaging cell line	No. of patients
016	Phase I study in patients with recurrent metastatic squamous cell carcinoma of the head and neck using SCH 58500 (rAd/p53)	Head and Neck Cancer	Institute of Cancer Research/Royal Marsden Hospital	SEP 96	DEC 96 CLOSED	Adeno-virus	p53	Human embryonic Kidney cell line 293	–
017	Gene therapy for Cystic Fibrosis Delivery to nasal epithelium and lung by nebulisation of the pCFICFTR/#67	CF Lung and Nasal Trial	Royal Brompton Hospital	NOV 96	NOV 96 CLOSED	Liposome	CFTR # 67	–	16
018	A Phase I dose-escalation study of intratumoral injection with modified HSV Type I (ICP 34.5-) into primary and recurrent malignant glioma	Glioblastoma	Beatson Oncology Centre, Glasgow	DEC 96	OCT 97	Retro-virus	ICP34.5 deleted	BHK 21/C13	9
018A	A study of the potential for efficacy of the modified Herpes simplax Virus (ICP34.5-) virus 1716 following intra-tumoural injection into primary malignant glioma	Glioblastoma	Beatson Oncology Centre, Glasgow/ Institute of Neurological Sciences, Glasgow/ Queen Elizabeth Hospital, Birmingham	JUL 99	JUN 00	HSV	ICP34.5 deleted	BHK 21/C13	12
018B	A study of the safety of the modified Herpes simplex virus (HSV 1716) when injected into tumour bearing brain following resection of recurrent or newly diagnosed high grade glioma	Glioblastoma	Beatson Oncology Centre, Glasgow.	NOV 00	APR 01	HSV	ICP34.5 deleted	BHK 21/C13	9

GTAC No.	Protocol Title	Details	Centre	Outline Approval	Trial Started	Vector	Gene	Packaging cell line	No. of patients
019	GTI 0115 radiation and infection of murine cells producing HSV TK vector followed by intravenous ganciclovir against the efficacy of surgery and radiation in the treatment of newly diagnosed previously untreated glioblastoma (tumour site)	Glioblastoma	Beatson Oncology Centre, Glasgow/ Institute of Neurological Sciences, Glasgow	MAR 97	Trial withdrawn	Retro-virus	TK	PA317	–
020	A clinical trial with Ad-5CMV-p53 vector in patients with ascites formation	Gastrointestinal cancer/ malignant cancer ascites	Royal Marsden Hospital, London	APR 97	CLOSED	Adeno-virus	P53	293 cell line	1
021	Phase II study of immunotherapy of advanced breast cancer by repeated intramuscular injection of recombinant vaccinia viruses containing sequences coding for human MUC-1 and IL2 (TG1031)	Breast Cancer	Guy's Hospital, London	NOV 97	JUN 98	Vaccinia virus	MUC-1 IL2	–	14
022	A multiple ascending dose study evaluating the safety and thegene transduction into malignantcells after the administration of EIA-lipd complex by intra-peritoneal administration inpatients with epithelial ovariancancer who over express HER-2/neu	Ovarian Cancer	The John Radcliffe Hospital, Oxford Guy's and St Thomas's Cancer Centre, London Royal Marsden Hospital, London. St George's Medical School, London	SEP 97	JAN 98 CLOSED	Lipid complex	E1A HER2/ neu	–	22

GTAC No.	Protocol Title	Details	Centre	Outline Approval	Trial Started	Vector	Gene	Packaging cell line	No. of patients
023	A pilot study of recombinant CEA vaccinia virus vaccine with post vaccination CEA peptide challenge in combination with 5-fluorouracil and folinic acid in the treatment of colorectal cancer (Phase I subcutaneous)	Colorectal Cancer	Queen Elizabeth Hospital, Birmingham	MAR 98	–	Vaccinia virus	CEA	–	–
024	A phase I study of intraperitoneal administration of a replication deficient adenovirus carrying a nitroreductase gene in ovarian cancer patients	Ovarian Cancer	City Hospital NHS Trust and University Hospital NHS Trust Birmingham	MAR 98	–	Adeno-virus	Nitro-reductase	–	–
025	A multiple ascending dose study evaluating the safety and gene transduction into malignant cells after administration of E1A-lipid complex by intratumoral injection with unresectable or metastatic head and neck tumours	Head and Neck	Royal London Hospital/ Charing Cross Hospital	–	Submission withdrawn	Lipid complex	E1A	–	–
026	A study of dose requirements, safety and local efficacy of intratumoral injection of the genetically modified non-virulent herpes simplex virus HSV ICP 34.5 negative mutant 1716 into accessible soft tissue nodules of secondary malignant melanoma	Malignant Melanoma	Glasgow Western Infirmary and Southern General Hospital, Glasgow	SEP 98	JAN 99	HSV1716	ICP34.5 deleted	–	5

GTAC No.	Protocol Title	Details	Centre	Outline Approval	Trial Started	Vector	Gene	Packaging cell line	No. of patients
027	The use of MetXia-P450 for the treatment of advanced breast cancer (Phase I/II intratumoral)	Breast Cancer	The Churchill Oxford	OCT 98	FEB 00	Retro-virus	Cytochrome P450	TEFLY-A	12
028	A phase I/II study of hepatic artery infusion with WTP53-CMV-AD in primary metastatic malignant liver tumours	Liver Cancer	Hammersmith Hospital, London	–	Submission Withdrawn	Adeno-virus	p53	–	–
029A	A Phase I/II pilot study of idiotypic vaccination for follicular B-cell lymphoma using a genetic approach (i.m.)	B-cell lymphoma	Royal Bournemouth Hospital and Royal South Hampshire Hospital, Southampton	MAY 99	NOV 99	Plasmid	Idiotypic DNA vaccination	–	20
029B	A pilot study of donor idiotypic vaccination for the purpose of targeted post-transplant immunotherpay following allogenic bone marrow transplantation for multiple myeloma	Multiple Myeloma	Royal Bournemouth Hospital and Royal South Hampshire Hospital, Southampton	MAY 00	AUG 00	Plasmid	Idiotypic DNA vaccination	–	3
029C	Phasel/II study of Idotypic vaccination for multiple myeloma usinf a genetic approach (MMIFTT)	Multiple Myeloma	Royal Bournemouth Hospital and Royal South Hampshire Hospital, Southampton	APR 00	–	Plasmid	Idiotypic DNA vaccination	–	0
029D	Phase I/II study of idiotypic vaccination for chronic lymphocytic leukaemia uisng a genetic approach (CLLIFTT)	Chronic Lymphocytic Leukaemia	Royal Bournemouth Hospital and Royal South Hampshire Hospital, Southampton	APR 00	AUG 00	Plasmid	Idiotypic DNA vaccination	–	–

GTAC No.	Protocol Title	Details	Centre	Outline Approval	Trial Started	Vector	Gene	Packaging cell line	No. of patients
030	Use of a retrovirus carrying human cytochrome p450 for the treatment of ovarian cancer (Phase I intra-abdominal)	Ovarian Cancer	Northern General Hospital, Sheffield	FEB 00	AUG 00	Retro-virus	Cytochrome P450	TEFLY-A	6
031	Gene directed enzyme prodrug therapy for the treatment of head and neck cancer (Phase I intratumoral)	Head and Neck Cancer	CRC Institute for Cancer Studies, University of Birmingham	JUL 99	FEB 00	Adeno-virus	Nitro-reductase	PER-C6	1
032	Gene directed enzyme prodrug therapy for the treatment of liver cancer (Phase I intratumoral)	Liver Cancer	CRC Institute for Cancer Studies, University of Birmingham	JUL 99	FEB 00	Adeno-virus	Nitro-reductase	PER-C6	9
033	Phase I trial of immunotherapy with adenovirus-interferon-g in malignant melanoma (intratumoral)	Malignant Melanoma	St. George's Hospital	JUL 99	JAN 00	Adeno-virus	IFN-g	–	1
034	A phase II/III trial of chemotherapy alone versus chemotherapy plus Adp53 in ovarian and primary intraperitoneal cancer (intraperitoneal)	Ovarian Cancer	Royal Marsden Hospital/ Christie Hospital/ CRC Institute for Cancer Studies/ John Radcliffe Hospital	JUL 99	MAY 01 CLOSED	Adeno-virus	p53	–	1
035	Phase II trial of pre-operative intratumoral injection with an E1B attenuated adenovirus in patients with resectable head and neck tumours	Head and Neck Cancer	Beatson Oncology Centre, Glasgow	JUL 99	NOV 99 CLOSED	Adeno-virus	E1B deleted	–	1

GTAC No.	Protocol Title	Details	Centre	Outline Approval	Trial Started	Vector	Gene	Packaging cell line	No. of patients
036	The safety and effects of Ad5.1 mediated human FGF-4 gene transfer in patients with peripheral arterial occlusive disease (PAOD) Fontaine stage III (Phase I i.m.)	Peripheral Arterial Occlusive Disease	St George's Hospital, London	OCT 00	AUG 01	Adeno-virus	FGF-4	PER.C6	0
037	A Phase III study of quadruple HAART follwed by double-blind randomisation to HIV vaccination wwith ALVAC-HIV and Remune or placebo	HIV	Chelsea & Westminster Hospital, Royal Free Hospital, Brighton General Hospital, University Hospital of Wales Cardiff	MAY 00	–	Canary-pox	HIV-1 env, gag	–	–
038	A Phase I, open label, dose escalation trial to assess the safety and immunogenicity of DISC-GMCSF in patients with metastatic melanoma	Malignant melanoma	Churchill Hospital, Oxford Royal Marsden Hospital, London	MAY 00	SEP 00	HSV-2	hGMCSF (Vero-derived)	CR2C9	10
039	Gene therapy protocol for the evaluation of the safety, biodistribution and efficacy of Trovax in patients with metastatic colorectal cancer (Phase I i.m.)	Colorectal cancer	Christie Hospital NHS Trust, Manchester	OCT 00	FEB 01	Vaccinia	Human oncofoetal antigen 5T4	Specific antigen free Eggs (SPAFAS	13
040	A Phase I dose escalation trial of an E1B attenuated adenovirus as an intravesical therapy for recurrent superficial/muscle invasive bladder cancer	Bladder cancer	St James's University Hospital, Leeds	JUL 00	–	Adeno-virus	E1B deleted	–	–

GTAC No.	Protocol Title	Details	Centre	Outline Approval	Trial Started	Vector	Gene	Packaging cell line	No. of patients
041	Randomised multi-centre trial evaluating two different vaccination schedules of MVA-MUC-1-IL-2 in women with metastatic breast cancer (Phase II i.m.)	Breast cancer	Guy's Hospital, London	Application withdrawn	Not started withdrawn	Vaccinia	MUC-1, IL-2	–	–
042	Phase I study of melanoma poly-epitope DNA and melanoma poly-epitope modified vaccinia Ankara in patients with melanoma	Melanoma	The Churchill Hospital, Oxford	JUL 00	APR 01	Vaccinia	Mel3 (melanoma antigens)	N/A	7
043	A phase I/II trial of polyHER2 neu-a polyepitope DNA vaccine encoding HER-2 epitopes in the treatment of epithelial cancers (i.m.)	Breast cancer	St James's University Hospital, Leeds	REJECTED		–	HER-2 epitopes	–	–
044	Treatment of leukaemic relapse after allogeneic stem cell transplantation by HSV-tk transduced donor lymphocyte transfusions	Chronic myeloid leukaemia	Hammersmith Hospital, London	OCT 00	–	Retro-virus	HSV-tk	–	–
045	Phase I clinical gene therapy protocol for X-SCID	X-SCID	Institute of Child Health, London	JAN 01	JUL 01	Retro-virus	Common gamma chain	PE13	1
046	Phase I gene therapy protocol for X-CGD	X-CGD	Institute of Child Health, London	DEC 00	NOV 01	Retro-virus	Gp91-phox	293	1

GTAC No.	Protocol Title	Details	Centre	Outline Approval	Trial Started	Vector	Gene	Packaging cell line	No. of patients
047	A phase I, Randomised, Double-blind, Placebo Controlled, Escalating Dose, Multicentre Study of Ad2/Hypoxia Inducible Factor Gene Transfer Administered by Intramyocardial Injection During Coronary Artery Bypass Grafting Surgery in Patients with Incomplete Revascularisation	Coronary artery disease	John Radcliffe Hospital, Oxford	DEC 00	–	Adeno-virus	HIF-1a	–	–
048	A randomised phase I trial of intravenous CI-1042 with or without entanercept in patients with metastatic carcinoma	Metastatic carcinoma	Hammersmith Hospital, London	DEC 00	–	Adeno-virus	p53	–	–
049	A phase I/II Study of Immunotherapy for Patients with Metastatic Melanoma Using Dendritic Cells Transfected with a Plasmid Encoding Two Melanoma Antigens	Metastatic Melanoma	CRC Institute for Cancer Studies, Birmingham	FEB 01	–	Plasmid complexed with peptide	MART-1 gp-100		0
050	A Phase II Trial of Preoperative Intratumoural Injection with HSV1716 in Patients with Resectable Squamous Cell Tumours of the Head and Neck	Head and Neck Cancer	Canniesburn Hospital, Switchback Road, Glasgow, G61 1QL	MAY 01	–	Herpes Simplex Virus	ICP34.5 deleted	BHK-21/C13	–
051	A multicentre, randomised, double-blind, placebo controlled, dose-response study to evaluate the efficacy and safety of Ad5. 1FGF-4 in patients with Stable Angina	Coronary Artery Disease	Papworth Hospital, Cambridge	MAY 01	–	Adeno-virus (E1 deleted)	FGF-4	PER.C6	–

GTAC No.	Protocol Title	Details	Centre	Outline Approval	Trial Started	Vector	Gene	Packaging cell line	No. of patients
052	A phase I study to evaluate the safety, tolerability and immunogenicity of two administrations of either plasmid DNA (pSG.HBs) versus placebo or modified vaccinia virus Ankara (MVA.HBs) versus placebo, followed by two boost administrations of MVA.HBs expressing hepatitis B surface antigen in healthy male volunteers	Hepatitis B Vaccine Trial	TNO BIBRA International Surrey	AUG 01	–	Modified Vaccinia Virus Ankara (MVA) & naked plasmid	HBsAg	MVA: Chicken embryo fibroblasts Plasimd: E. Coli DH5α	
053	A pilot study of the safety and immunogenicity of a candidate HIV-1 clade A DNA vaccine, pTHr.HIVA, given by needle injection into the deltoid muscle in HIV-1-seropositive subjects receiving highly active antiretroviral therapy	AIDS	John Radcliffe Hospital, Oxford	MAY 01	–	Naked Plasmid	HIV-1 clade A gag and 25 HIV-1 gag/pol/ env/nef CTL epitopes	E. Coli DH1	–
054	A Phase II, Randomised, Double-Blind, Placebo-controlled, Parallel Group, Efficacy and Safety Study of NV1FGF in Patients with Severe Peripheral Artery Occlusive Disease	Peripheral Artery Occlusive Disease	St. George's Hospital, London	AUG 01	–	Naked Plasmid	FGF-1	E. Coli XAC-1	–
055	Gene directed enzyme prodrug therapy for the treatment of prostate cancer (Phase I intratumoral)	Prostate Cancer	CRC Institute for Cancer Studies, University of Birmingham	APR 01	SEP 01	Adeno-virus	Nitro-reductase	PER-C6	0

GTAC No.	Protocol Title	Details	Centre	Outline Approval	Trial Started	Vector	Gene	Packaging cell line	No. of patients
056	A Phase II, Multicentre, Double-Blind, Placebo-Controlled, Dose-Finding Study of ZYC101a in the Treatment of High-Grade Squamous Intra-Epithelial Lesions of the Uterine Cervix	AnoGenital Neoplasia III	Hammersmith Hospital, London	UNDER REVIEW	–	Plasmid	HPV E6 & E7	–	–
057	A Phase I, Multidose Study to Evaluate the Safety of Intramuscular Injections of HER-2 DNA in Patients with Metastatic Breast Cancer	Breast Cancer	Hammersmith Hospital, London	OCT 01	15 OCT 01	Plasmid	HER-2	–	0
058	The Use of a cDNA Vaccine Encoding the Human MUC1 Gene in the Treatment of Patients with Advanced Breast Cancer – A Phase I/II Study	Breast Cancer	ICRF, Guy's Hospital, London	AUG 01		Plasmid	MUC-1	–	–
059	TA-HPV recombinant vaccinia virus expressing the human papillomavirus 16 and 18 E6 and E7 proteins: Application to amend currently approved protocol to add a clinical trial involving a prime-boost strategy of TA-CIN administered in association with TA-HPV in high grade ano-genital intraepithelial neoplasia (AGIN) patients (PB-HPV/01).	Cervical Cancer	University of Wales, Cardiff, St. Mary's Manchester; Addenbrooke's, Cambridge	JUL 01	AUG 01	Vaccinia	E6 & E7 HPV	MRC-5	8

GTAC No.	Protocol Title	Details	Centre	Outline Approval	Trial Started	Vector	Gene	Packaging cell line	No. of patients
060	Study of Transfection Efficacy and Safety of MetXia-OB83 in patients with cutaneous lesions of breast cancer or melanoma	Breast Cancer	The Churchill Hospital, Oxford	JUL 01	–	Retro-virus	P450	TEFLYRD	–
061	An upward titration study of transfection efficacy and safety of Metxia-OB83 in patients with adenocarcinoma of the prostate	Prostate Cancer	The Christie Hospital, Manchester	OCT 01	–	Retro-virus	P450	TEFLYRD	–
062	First Administration to Man of an Oncolytic Herpesvirus Vector Containing a Transgene for Granulocyte Macrophage Colony Stimulating Factor (OncoVex^{GM-CSF}) – A Study of its Safety, Biodistrubution and Biological Activity	Melanoma, Breast, Head & Neck, cancer, Non-Hodgkins Lymphoma	Hammersmith Hospital, London	OCT 01	–	Herpes Simplex VIrus	ICP34.5-deleted ICP47-deleted Human GM-CSF	BHK 21c13	0

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